CONTROLLED CLINICAL TRIALS

CONSIDERATIONS ON THE NUMBERS OF PATIENTS REQUIRED

A STUDY BASED ON MAMMARY CARCINOMA

H. P. J. M. BEEREPOOT

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To Hanneke

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'For the great enemy of the truth is very often not the lie – deliberate, contrived and dishonest – but the myth – persistent, persuasive and unrealistic.

Too often we hold fast to the cliches of our forebears. We enjoy the comfort of opinion without the discomfort of thought.'
President John F. Kennedy at
the Yale Commencement Ceremony
in July, 1962.

CHAPTER I. INTRODUCTION

§ 1. *Why controlled clinical trials on mammary carcinoma?*

A survey of the literature shows that in spite of a great number of pertinent publications, uncertainty remains concerning the treatment of choice for a given patient with a given mammary carcinoma. There are numerous reports on very careful studies, but after 50 years no fundamental improvement of results has in fact been achieved. It can therefore be deduced that the retrospective methods of investigation so far practised have been insufficient to demonstrate possible differences in results of various therapeutic regimens.

Moreover these retrospective methods are open to serious criticism because the comparability of the groups of patients treated with different therapies cannot be guaranteed.

There is obviously a need for investigations to evaluate various methods of treatment on the basis of statistically sound patterns.

In The Netherlands, it was the late Professor Moeys who, some 20 years ago, recognized the necessity of prospective studies on the treatment of mammary carcinoma, and instituted such a study.

Moeys' initiative became the basis of the present study. However, as will appear, the material of Moeys does not completely meet modern requirements for prospective studies on mammary carcinoma. In the international literature (cf. Ch. V), the first advocates were such investigators as Kaae (in 1951), Paterson (in 1955), and Nissen-Meyer (in 1957).

Armitage (1968) wrote on this subject: 'The main requirement of a method for comparing the therapeutic effects of different treatments is that there must be no systematic bias tending to favour one or other treatment. If treatments are to be compared on different groups of patients we must try, as far as possible, to ensure that these groups are similar in all relevant respects, except in the treatments they receive.'

For those familiar with statistical methods, it is a well established fact, that where statistical investigations are needed in evaluating the results of different treatments, reliable conclusions can be obtained only by means of carefully performed clinical trials.

A controlled clinical trial here in brief to be called 'clinical trial' is an investigation in which two or more methods of treatment for a well-defined disease are compared on similarly composed groups of patients. The trial should aim at answering a definite question and meet the requirements for a sound statistical analysis.

As clinical trials yield results which warrant reliable conclusions, they can be compared with other studies. Unlike other methods of investigation, these trials are designed on the lines of a laboratory experiment. Paterson (1962) wrote in this context: 'The term 'clinical trial', was advised by the Medical Research Council years ago to avoid the open use of the blunter term 'experiment'. This was wise; but let us not forget among ourselves that clinical trials are true experiments, calling for just as rigid a discipline as the laboratory experiment'.

To make a comparison possible between the results of different clinical trials, an exact description of the categories of patients and methods of treatment under investigation must be available. For further details on clinical trials cf. Ch. III. At present, a large number of investigations are being carried out in the field of mammary carcinoma, and these include a number of clinical trials. The World Health Organization (1968) has many studies on record.

In an article by Flamant (1969) 161 clinical trials on cancer are noted, of which 34 are on breast cancer.

A number of clinical trials have already been completed, some of these concerned essentially curative therapies (Kaae 1965, 1968; Paterson 1959a, 1959b, 1962; Nissen-Meyer 1965, 1968), while others concerned metastatic carcinoma (Atkins 1960).

§ 2. *The aims of the present study*

It was our intention to collect a group of patients with mammary carcinoma who had been treated largely in accordance with a uniform plan and to evaluate retrospectively the various methods of treatment.

With the collaboration of many colleagues, we succeeded in collecting 1500 patients of this type. This group of 1500 patients could be divided into several homogeneous subgroups. Since all the patients in each subgroup had been treated according to one fixed criterium it seemed possible, initially, to find a few comparable groups of patients in this material, treated with different therapies. Moreover we expected a part of the material, sampled by Moeys, would meet the requirements of a clinical trial.

In processing our material we found that a considerable diversity of therapies had been used. Distinctions had to be made according to the usual surgical therapies such as simple mastectomy, simple mastectomy with axillary dissection, radical mastectomy and the techniques of irradiation. In a proportion of patients moreover, a radiological menopauze was prophylactically provoked, or hormones or cytostatic drugs were prophylactically given. Both surgeons and radiologists had accepted their own fixed plan of therapy. Except in the series of Moeys, we do not know, however, which indications may have caused them to deviate from this plan. When evaluating treatments, only definite combinations of surgical, radiological and drug treatments can be

regarded as a unity, and a variety of combinations has to be considered. Exact differentiation of all variations of therapy in our material would cause such fragmentation of the material that a statistically sound investigation of the results of various therapies would be impracticable because of insufficient numbers of patients in each therapy-group.

In solving this problem it seemed rational to sample even more patients with mammary cancer treated according to particular schemes until a sufficient number in each subgroup was reached.

Many examples can be found in the literature which show the possibility of sampling large series of patients with mammary cancer (cf. table I-1 Berniczei, 1962).

TABLE I-1. *The number of patients included in retrospective studies on mammary cancer. A survey of the literature (from Berniczei M. 1962, table I).*

Author	Year	Number of patients
Berven	—	25 000
Kaae, E	1908–45	189
Haagensen	1915–19	128
(Presbyterian-Hospital)	1920–24	127
	1925–29	160
	1930–34	225
	1935–39	314
	1940–42	181
Taylor	1894 until 1904	468
	1911–14	103
	1918–20	134
	1921–23	183
	1924–26	208
	1927–29	220
	1930–32	231
	1933–35	328
	1936–40	600
Sedgwick and St. Ville	1941–50	292
Shimkin	1918–44	899
Nohrman	1936–41	1042
Adair	1935–42	3836
Wanke	1908–52	1098
Diethelm	1913–45	698
Berkson	1910–14	2363
(Mayo-Clinics)	1950–54	1416
Lewison	1935–40	220
(J Hopkins-Hospital)	1941–45	259
Robbins	1940–43	1281
(Memorial Center Hospital)	1950–55	2168
McWhirter	1941–47	1882
Harrington, W. (Material of the Mayo-Clinics)	1910–44	8224
Warren and Tompkins	—	769

Author	Year	Number of patients
Baclesse	1935–46	77
	1958	310
Williams	—	100
Watson	1932–43	645
	1944–52	1055
Zaunbauer (Wiener I Chir Klinik)	1949–53	244
Urban	1959	76
Kohler	—	290
Kirsch	1958	347
Ryan	1935–41	1399
	1942–48	2123
Gray and Anglen	1939–53	278
Sicard	—	192
Abramson, Clifton, Slagle	1931–39	98
	1940–51	189
Koulumies	1936–47	544
	—	360
Widow and Huber	1949–54	229
Hickey, R C	1926–49	1661
	—	913
	—	444
	1956	431
	—	182
Treves and Holleb	1939–49	149
(Memorial Cent for Cancer)	—	219
Antonellis (Myers Clin)	1959	121
Miller and Pendergrass	1923–43	1029
Ravnihar	1945–54	641
Alrich, Liddle, Morton	1929–51	448
Gould, E A , and H H Kerr	1955	241
Arner	1955	1652
Hendrick, J W.	1933–51	562
Edward, M L.	1958	253

From our study, however, it appears that unselected sampling of patients will not help to solve existing problems of treatment (cf. Ch. II). Indeed, it seems impossible to come to reliable conclusions concerning different therapies, using our material, even if it was possible to extend it considerably.

Margaret Merrell (Bradford Hill,1967) has wisely observed: 'large numbers in themselves are worse than useless if the groups are not comparable, since they encourage confidence in an erroneous opinion'.

Meanwhile, because of the diversity in therapeutic conceptions existing in The Netherlands, The Netherlands' Cancer Organization decided to found a committee to discuss the treatment of mammary carcinoma (van Slooten, Breur, Hampe, Nelemans, Rümke, Schwarz, Thomas, Zwaveling, Beerepoot, 1968). It is the aim of this committee to lay down guidelines concerning the treatment of mammary carcinoma and to study the possibilities of executing a clinical trial in The Netherlands.

Partly as a result of discussions in this committee the Author concluded that, when planning a clinical trial it is important first to have some idea of the number of patients required.

After having made a computation of the number of patients required for a definite clinical trial, we concluded that it is upon this number that the practicability of a clinical trial concerning mammary carcinoma largely depends.

Some people are still very vague about this problem.

Truelove (1964) states: 'In general it is worth working with fairly large numbers although there are special circumstances where the results should be obtained with the maximum economy'.

Bradford Hill (1967) wrote on this subject: 'The well-controlled and well-reported experiment does not, as is sometimes thought, demand vast numbers.

If the groups are strictly comparable, then often a total of 50 to 100 cases, and sometimes very much less, will provide sufficient evidence. The actual numbers must, of course, depend upon the problem at stake and upon the magnitude of difference between the treatment and control groups that is to be expected or is actually observed'.

In this study we want to get an impression of the real numbers of patients required on statistical grounds in executing a clinical trial and how these numbers can be influenced by variations of design of the trial (cf. Ch. III §3, §6). Apart from these statistical considerations it was our aim to underline any other difficulties, arising in the study of the treatment of mammary carcinoma.

As we already mentioned, it may be necessary not to study the different treatments on all patients with mammary carcinoma as a whole, but on homogeneous subgroups. These are drawn up according to such characteristics of the tumor or the host, as may influence the course of the disease. The number of these characteristics is so great, that it must be realized, that it is possible the disease will be influenced far more by them than by therapy. Even when the patients involved in a trial constitute a homogeneous subgroup of the mammary carcinoma patients, there is always some variety left.

It is therefore necessary to assign the different therapies by randomization. If randomization is performed over the total group of patients available, it is possible, that within several subgroups the numbers of patients with definite characteristics allocated to the therapies compared differ considerably. For this reason Armitage (1968) recommends using a separate randomization list for each subgroup. From these considerations our approach will become much clearer as we study the number of

patients required to get statistically reliable conclusions concerning each subgroup.

In considering the extent of our material, it became clear to us that although the data drawn from it were inadequate for a comparison of treatments yet it could be used in planning a clinical trial, particularly in estimating the number of patients required. The reliability of these estimates, of course, depends on the representativeness of this material for mammary carcinoma patients in general (cf. Ch. II §4). In this study a survey is given of the factors determining the number of patients required in executing a clinical trial to evaluate different treatments for mammary carcinoma (cf. Ch. III). In addition, a method is described of estimating the requisite number of patients. This method is applied to our collection of 1500 patients with mammary tumors to get an impression of the number of patients required to solve particular problems concerning the treatment of mammary carcinoma. For this purpose nearly all the data considered in our series have been recorded in frequency tables.

In an attempt to gain an impression of the influence of coincidences between several characteristics of the tumor or the host on our computation, contingency tables have been worked out for 15 frequently appearing characteristics (cf. Appendix Part I).

However, anybody who is interested in planning a controlled clinical trial on mammary carcinoma should use preferably the figures of his own series of patients, in applying our computation.

To illustrate our approach, a number of completed clinical trials concerning mammary carcinoma are analysed according to our criteria (cf. Ch. V). An evaluation is given of the possibility of solving particular problems with the help of the clinical trials concerned. Because in the clinical trials executed so far the only criteria used are those that can be expressed in absolute or relative figures, our examples are worked out on the basis of such criteria i.e. 5 years mortality, 5 years recurrence rate.

General aspects of the organization as well as the ethical problems of a clinical trial are not considered to be within the scope of this study. Considerations about the organization of clinical trials can be found in the booklet of Flamant (1970). Ethical guidelines are laid down in a Statement of the Medical Research Council (1962–63) and in the Declaration of Helsinki (1964).

We investigated the possibility of obtaining from our data an impression of the course of mammary carcinoma.

Although we realize the great importance of records on this subject in the evaluation of methods of treatment it is not considered to be within the scope of this study.

'In the evaluation of a given procedure it becomes apparent only too often that, in recording some obvious and fundamental data, no provision has been made to establish the starting-point. Many statistics become non-comparable, and therefore often useless, because different criteria are applied'.
Schmidt (1967), in his inaugural address.

CHAPTER II MATERIAL AND METHODS

§ 1. *Introduction*

The collaboration of many colleagues made it possible to pool documented material of about 1500 patients with malignant disease of the breast in The Netherlands. The material was obtained from centres in Tilburg (including Moeys' series), Arnhem and Leeuwarden (cf. table II-I). The patients received their first therapy during the period 1947–1966.

§ 2. *The trial of Moeys*

Moeys' trial was so arranged that therapy in his own clinic consisted exclusively of simple mastectomy with postoperative irradiation according to McWhirter's method, while the other clinic in Tilburg used only radical mastectomy with postoperative irradiation. In keeping with this design however, the possibility of preselection is left open, as general practioners familiar with the organization of Moeys' trial may well have selected patients according to their opinion about the most suitable therapy.

For these reasons we abandoned our previous plan to draw conclusions from the results of Moeys' trial.

§ 3. *Survey of the entire material*

After Moeys' departure from Tilburg in 1958 the trial was not continued. The manner of registration was not changed, however.

To get a suitable group of patients, the whole series from Tilburg, and thereafter all the patients at the centres in Arnhem and Leeuwarden were included in our series. (Specifications cf. tables II-1 and II-2).

TABLE II-1. *The distribution of the patients over the three centres.*

CENTRE	Numbers of patients	%
Tilburg	643	45.5
Arnhem	314	22.2
Leeuwarden	460	32.3
Totals	1417	100.0

An additional 89 cases of malignant disease of the breast are registered but were not included in the material, while their inclusion would disturb the uniformity of the series (cf. table II-2).

TABLE II-2. *Survey of cases not included in the material (percentages on total number of entire material: 1506 cases).*

DIAGNOSIS	Numbers of patients	%
Breast carcinoma in males	7	0.5
Bilateral breast cancer*	36	2.3
Simultaneous breast carcinoma and other carcinoma (except skin carcinoma)	19	1.2
Distant metastases of carcinoma other than mammary, located in the breast	7	0.5
Sarcoma	20	1.3
Totals	89	5.8

* Patients noted as having metastases in the contralateral breast are not included.

§ 4. *Methods of recording and manipulating data*

To record the data of our series of patients we used the form 'Insertion (Mamma)', introduced by the Clinical Stage Grouping (1960–1964) of the Union Internationale contre le Cancer (cf. Appendix Part V). This form is based on the International TNM classification, in which the clinical stages of mammary carcinoma have been placed on record (cf. Ch. III §8).

Of the data on these patients we recorded as follows those characteristics that could have influenced the course of the disease:

1. The data of Moeys' trial were first recorded partly on a form designed by Moeys and partly on clinical records. All these data have been taken over by the author on the 'Insertion (Mamma)' form.
2. The remaining data of Tilburg and the data of Arnhem and Leeuwarden were for the most part directly recorded on the aforementioned 'Insertion (Mamma)' form.

A number of data were recorded on clinical records and have been taken over by the author on the 'Insertion (Mamma)' form. In total, 119 data per patient were encoded and punched into 80 columns-punch cards, which were further processed with the computer IBM 360/50 of the University Computer Centre at Nijmegen. 4 punch cards were used per patient.

Using the Cross-tab 2 program the data were tabulated in frequency tables (table f1–f50) and two-way contingency tables (table f_c1–f_c99).

In these tables the frequencies are supplied in absolute figures of totals whole series and in absolute figures and percentages of row and of column totals of totals noticed data. Finally per datum percentages are supplied of the noticed data. (cf. explanation f_c tables, Appendix Part I).

The data of our material considered usable for our purpose are arranged in such a way as to be suitable in determining the number of patients required for a clinical trial. Except for data indicating the 'curative operability' of the patient, data on the course of the disease after starting treatment are not included as they are not necessary for determining the required number of patients.

§ 5. *Uncertainties in the material*

In using our data for a determination of the requisite number of patients in a clinical trial, one must remember the uncertainties as to whether our material was representative of mammary carcinoma in general.

Some known uncertainties are described below:

a. The material was obtained by pooling the groups of patients of three centres (Tilburg, Arnhem and Leeuwarden). The geographical situations of these centres do not ensure that all the patients with mammary carcinoma in the respective districts are in fact treated at the centres. Some patients may have received their treatments at University Clinics. This means no assurance can be given that the material gives an exact picture of the whole population of patients in the catchment areas of the centres concerned. As a result, a selection-factor of unknown magnitude has been introduced.
b. Scores of physicians recorded data on patients, including evaluation of the tumor stage. As these records were not verified by a coordinating committee, 'observer variation' must be assumed to have had a powerful influence.
c. A proportion of data was first recorded on a form designed by Moeys or on the clinical record-cards (cf. Ch. II §4). These data have been taken over on the 'Insertion (Mamma)' form by the author and thus misinterpretations of the original records might be introduced.
d. Our data were taken from the clinical records of surgeons and radiologists. It is possible that a patient could have been seen only at the out-patient clinic, in which case she would of course be absent from our material.
e. We obtained our series by pooling the material of several centres in order to obtain larger numbers of patients. An unknown number of uncertainties regarding the composition of each of these series had to be accepted.
f. Although the recording of data always gave an impression of accuracy, a considerable number of data were found to be lacking. It is understandable that this introduces a source of uncertainty of incalculable magnitude. Thus, for a proportion of the absent data one might assume that the symptom under consideration was absent.

It is for instance understandable that a clinician examining a tumor classified as stage I, does not record the fact that the supraclavicular glands are not affected. In that case, this symptom would be recorded as 'unknown' in this study. On the other hand, in examining a tumor classified as stage IV, it may well be that slight adhesions to the skin or the substratum are not recorded. One may tend to remove the cases with 'unknown' data from the material in order to enhance the reliability of the study. We decided not to do so, as this possibly implies also the introduction of a selection factor, the magnitude of which cannot be estimated. For example: if all cases in which affection of the supraclavicular glands was not recorded were removed from the material, this would involve far more stage I cases than stage III cases. Consequently, a bias would be introduced in the frequency distribution of the stages.

For this reason we preferred to state the number of 'unknowns'* with each datum, calculating the relative frequencies only for the 'knowns'. Proceeding in this way the investigator hopes that the relative frequencies in the group of unknowns will equal that in the group of knowns.

Nevertheless, a number of about 150 patients has not been included in our 1500 patients because the available data were too incomplete on essential points to be processed. The fact that no complete record was made of a patient may mean that this was not considered important for that particular case because of an expectedly benign lesion or by reason of the extent of the disease or bad general condition. New forms of selection may thus have been introduced.

* noted as 'other' in the tables of the appendix.

CHAPTER III. ESTIMATING THE NUMBERS OF PATIENTS REQUIRED FOR A CLINICAL TRIAL

§ 1. *Introduction*

A controlled clinical trial must fulfil a number of conditions to allow of objective and reliable comparison. Every clinical trial needs careful preparation, of which only a general description can be given within the scope of this paper. As a rule, the basic question will be an incompletely specified medical problem, e.g. whether ovariectomy is useful in the treatment of mammary carcinoma patients who have not yet or who have only recently entered the menopause.

The problem will first have to be described more accurately. The criterion 'not yet or only recently entered menopause' must be defined. One must further define the way in which the ovariectomy is to be performed and the additional methods of treatment to be administered. Once the problem has been defined accurately sufficiently from the medical point of view, a more detailed statistical specification will generally be necessary as well. For instance, in regard to ovariectomy the physician will require a decision valid for menstruating women suffering from a mammary carcinoma in a particular stage of development. The statistician can approach this problem only if the population of women among whom the investigation is to be carried out is determined more precisely from the geographical and chronological points of view, e.g.: patients with mammary carcinoma living in The Netherlands on January 1st, 1970, who fulfil the conditions stated.

The population about whom a decision is required may consist of far more patients than are necessary for an adequate trial. In that case the trial will have to be carried out with a representative sample from the patient population. This sample must be selected in such a way as to have a composition similar to the population in certain general characteristics, but otherwise to be at random. If the sample is composed in this manner, the conclusions drawn from the clinical trial will in principle be valid for the population as a whole.

However, in respect of mammary carcinoma the number of patients available at a given time will generally be insufficient for the organization of a trial. If so, all suitable patients applying for treatment successively during a given period will have to be included in the trial. The possibility must then be borne in mind that the patients

available for a trial constitute a select group in regard to the reaction to one or more of the methods of treatment to be compared. Once it has been decided which patients will be included in the clinical trial and what methods of treatment will be compared, the methods of treatment must be so assigned to the patients that no single therapy is systematically 'favored' or 'neglected'. This means that we must prevent the group of patients to be subjected to a particular method of treatment differing systematically from other patients in the trial in regard to factors which may affect the success of treatment. This can be achieved by random assignment of methods of treatment; in principle, by drawing lots.

The method of drawing lots depends on still other factors, e.g. whether all patients are available at the same time or will become available successively. For further details cf. Appendix Part VI.

In order for the results of the various methods of treatment to be compared, criteria permitting useful comparison of the results must be defined before the experiment starts. In principle, these criteria consist of data concerning the groups of patients, for instance: mean survival time, or mean percentage of patients in whom a certain phenomenon (death, recurrence) occurs within a certain period. More than one criterion may be involved in the discussion. Since the results, though not differing in one aspect, may nevertheless differ in another, a more differentiated conclusion concerning the methods of treatment compared can be achieved in this way.

§ 2. *Statistical tests*

When the groups of patients used to compare the methods of treatment are selected at random from the available patient population, these groups may show 'coincidental' differences of factors which may influence the treatment. A decision that the methods of treatment (in regard to a certain criterion) are not equivalent may then be made on the basis of differences in results actually due to differences occurring 'coincidentally' during the drawing of lots, e.g. differences in the general conditions of the groups of patients treated. In Statistics, a false conclusion of this nature is called an *error of the first order*.

By subjecting the finding to an adequate statistical test, dependent on the criterion of comparison applied, and by basing the conclusions on the result of this test, the probability of an error of the first order being made can be kept within previously defined limits, the *level of significance*. This is always possible, irrespective of the number of patients available.

A statistical test in regard to a particular criterion can, in principle, only lead to one of two conclusions: either

I. The methods of treatment compared are not equivalent. In this case, a difference has been demonstrated between the methods. The probability that this conclusion is false is less than the level of significance selected.

II. No difference can be demonstrated between the methods of treatment.

Conclusion I. is not synonymous with the conclusion that the methods of treatment are equivalent. It is possible for the effect of a small difference between the therapeutic

methods to be masked by the effect of a 'coincidental' difference in compositions between the two groups of patients.

Every test with a defined level of significance has its *power*. This power is the probability of an existing difference actually being detected. In this connection we call a difference *detected* if the null hypothesis that no difference exists after testing is rejected. The power depends on:

a. the test applied,
b. the level of significance (the higher the level of significance, the greater the power),
c. the number of patients in the trial and their distribution between the various methods of treatment, and
d. the degree of actual difference in effect between the methods of treatment compared.

The difference in effect under d. concerns the difference in parameter applied as a criterion (e.g. relative frequency of survival, or mean survival time) in the entire patient population considered. When the experiment is being planned, this difference is always unknown. The power must be interpreted as a function of this unknown difference. Knowledge of the power of the test to be applied is essential for the design of a clinical trial and in particular for estimating the number of patients required.

This knowledge can be applied in various ways:

a. We can determine the degree of difference in effect which we want to demonstrate by the experiment to a reasonable certainty, e.g. a probability of 95%. Once the test and the level of significance to be applied are defined, this results in a minimum number of patients required per method of treatment. This minimum is henceforth called the statistically required number of patients. It depends on the test used, the level of significance, the difference in effect to be detected, and the desired probability that this difference will be detected.
b. If method a. requires prohibitively large numbers, we may also base our trial on the number of patients becoming available within a reasonable period of time. The power of the test then indicates the degree of minimal difference in effect one is able to demonstrate with a probability of e.g. 95%. When in this connection we speak of detecting a particular difference in effect, this only means that we have demonstrated that the difference in the population is not $= 0$. It does not mean, therefore, that the difference is of a particular degree.

In the following paragraphs we shall discuss three statistical tests applicable for the analysis of clinical trials. We shall limit ourselves to descriptions of the principles of the tests and to tables of the numbers of patients required. For further details concerning the tests and the theoretical backgrounds to the tables, cf. Appendix Part VI.

Apart from the number of patients required the expected duration is also significant in planning for a trial. A particular test may be efficient in regard to the number of patients required but may take much longer to reach a decision than some other test requiring more patients. A discussion of the duration of trials can also be found in Part VI of the Appendix.

A certain population of patients suffers from a particular disease. For this disease two methods of treatment, A and B, may be considered. The result of the treatment is evaluated on the basis of a criterion such as death, recurrence or the development of metastases within a certain period after commencement of treatment. For the sake of clarity we shall for the moment assume that the criteria are, that the treatment has been 'successful' if the patient survives and 'unsuccessful' if he dies within 5 years after commencement of treatment. Let us call $P_A\%$ and $P_B\%$ the unknown proportions of patients in the population considered in whom method A and method B are successful.

We regard the methods of treatment as equivalent if $P_A = P_B$ and unequivalent if $P_A \neq P_B$. To check this we take two random samples from the population, both consisting of the same number S. The patients in one sample are treated by method A and those in the other sample by method B. If n_A patients in the first sample and n_B patients in the second sample show a certain effect within the period defined, the hypothesis $P_A = P_B$ will be rejected if $\frac{n_A}{S} - \frac{n_B}{S}$ is 'sufficiently large'. This 'sufficiently large' depends on the desired level of significance α. For further particulars, and a detailed example, cf. Appendix Part VI. If we also demand that the hypothesis $P_A = P_B$ should be rejected with reasonable certainty, for instance at least $(100 - \beta\%)$, if P_A and P_B have different, known values, this leads to a certain minimal value of S. This value S is listed in table S1, for $\alpha = 5\%$ and $\beta = 5\%$, for the values of P_A and P_B which are multiples of 10%. In order to give an impression of the value of S if a power of 90% is required, table S2 was calculated for $\alpha = 5\%$ and $\beta = 10\%$.

In the appendix we have also calculated the factor for a number of values of α and β by which the necessary number of observations from table S1 must be multiplied if a power other than 95% and/or different level of significance is desired. For $\alpha = \beta = 5\%$, we find that the S necessary with 5 year survival probabilities of 40 and 50% for methods A and B amounts to 642. If $\beta = 10\%$ were acceptable, this number would become $0.809 \times 642 = 519$ (cf. table S2) and if only a $\beta = 1\%$ were accepted, S would become $1.849 \times 642 = 1{,}187$ (cf. Appendix Part VI).

To limit the number of tables in our further discussion, we apply a level of significance $\alpha = 5\%$ and a power of $(100 - \beta) = 95\%$, the values usually accepted in statistical testing. Obviously the possible applications of these tables are limited to clinical trials in which the criterion of comparison is the proportion of patients who present a certain reaction within a certain period. Even within this design, the table does not supply complete information: it is only valid for experiments in which but two methods of treatment are compared. The eventuality of comparison of more than two methods of treatment, where the procedure is much more complicated, is not expounded in this study.

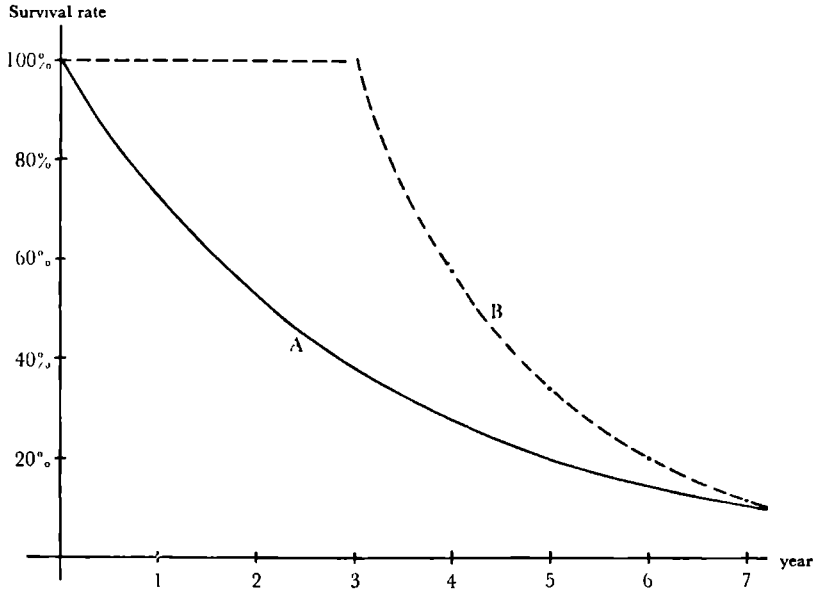
Another limitation of the table is that it is assumed that the two samples to be compared are of the same size. An experiment with equal numbers of patients in both treatment groups is admittedly more efficient than an experiment with unequal numbers but in practice it is possible that one of the two therapeutical methods can only be applied to a limited number (less than 50%) of the patients available, for instance due to lack of technical facilities. Strictly speaking, the table only applies

where the groups to be compared may be regarded as random samples from a population. The parameters P_A and P_B are defined in relation to this population. For instance, when all the patients available in a given area are included in the experiment, the group will have to be regarded as a sample of an imaginary population or it will have to be assumed that in every case there is the same probability P_A (P_B) that the patient will present the reaction within the period defined under treatment by method A (B).

At the beginning of this section we mentioned a criterion for evaluation of the results of therapy. This criterion must be defined primarily on medical grounds. If from the medical point of view several criteria are equally useful for deciding whether there is any difference between two methods of treatment, we may consider a choice on the basis of the numbers of patients required. If 5 year survival is selected as the criterion, the probabilities that patients survive for 5 years after treatment by methods A and B might be, say, 40% and 50% respectively. The number of patients required to detect this difference is 642 per treatment group. If the probability of local recurrence within 5 years is selected as the criterion, these probabilities may be 10% and 20% respectively and the number of patients then necessary to detect this difference amounts to 323 per treatment group.

Greater selectivity resulting in formation of more homogeneous patient groups may also lead to a reduction in the number of patients required (as explained at the end of Part VI of the Appendix) while the chances that the trial will supply answers to specific questions are even better with greater selectivity (cf. Ch. III § 6). In choosing the criterion we must further consider the fact that effectively different methods of treatment may differ not only in the chances of 5 year survival achieved, but also in the entire survival curve. Suppose the curve after treatment A is exponential (cf. Appendix Part VI), while after treatment B it remains practically horizontal for 3 years because metastasization is delayed by hormonal treatment.

FIGURE III-1. *The consequence of a difference in survival curve between treatment A and B.*



The difference in 3 year survival rates will then be considerable. If we further suppose that the sensitivity of the tumor to hormone treatment rapidly decreases after 3 years, the survival curve for treatment B would become exponential after this period and the two curves would rapidly approach each other. Had the 7 year survival rate been selected as criterion, it is probable that no distinct difference would have been detected, despite the fact that method B has marked advantages (cf. Figure III-1).

In planning a trial, a choice must ultimately be made. When the investigation involves an entirely new method of treatment, with no clear expectations concerning chances of survival, we may at the most consider a pilot trial with a small number of patients, e.g. only sufficient to allow detection of a difference of 30% in the chance of survival.

However, when the effect of an entirely new therapy is to be studied, a pilot trial of limited extent may be very useful because it obviates the danger of any important advantage of the new method escaping notice. If the new therapy proves greatly inferior, the number of patients treated by it is only small. If we can assess the difference in chance of survival which is maximally possible, if necessary after a pilot trial, we must determine the number of patients required by means of table S1. If this number is found to be too large, it would hardly be advisable to organize a trial. If the number is feasible, we are confronted with a dilemma. The larger the number of patients included in the therapeutic experiment, the smaller the difference in chance of survival detectable by the investigation and the clearer the conclusion that can be drawn.

If the number of observations is sufficient to detect a difference of e.g. 10% in survival chance, we may, if the trial does not yield a significant result, conclude that the difference in survival chance is 10% at the most. This maximum possible difference may be so small that no further study can be considered. On the other hand, a new trial may be started with a sufficient number of patients to detect the difference. This possibility makes it advisable when planning a trial to pay special attention to its practical feasibility. If a trial is on too large a scale, coordination between the participating centers may become a problem, it may be difficult to follow all patients, to establish cause of death in sufficient detail, etc. On the other hand trials with large numbers of patients do have the advantage of keeping us better informed concerning the effect of treatment on the course of the disease and giving us an impression of the complications likely to occur (Witts, 1964).

One must also remember that a trial not offering a 95% probability of detection of a particular difference in the 5 year survival rate may nevertheless have a fairly good power in regard to this difference (cf. Appendix Part VI table A1).

The examples worked out in this thesis are based on the assumption that differences in probability of survival of 10% or multiples thereof had to be detected. For this purpose, table S1 has generally been used (cf. Ch. IV).

For P_A and P_B we chose values approximating to the relative survival rates found in our material or in the reports of other investigators.

Table S1 is based on the χ^2 test for a 2×2 table.

In § 4 and § 5 we described two other test methods (for detailed descriptions cf. Appendix Part VI). With comparable alternatives these methods may require fewer patients than the χ^2 test. They may also lead to a conclusion in a shorter time.

Nevertheless in trials concerning mammary carcinoma, the χ^2 test was applied

as a general rule, its principal advantage being that it is less complicated, especially on the following points:

1. The criterion is simple: all that needs recording concerning the patients involved being whether they have died within a certain period and whether the mammary carcinoma may be regarded as the direct or indirect cause of death. The administrative work is therefore relatively light.

2. The number of patients required depends exclusively on the chances of surviving the period defined. No further assumptions concerning the distribution of the survival times need be made.

3. The duration of the trial can be estimated beforehand and with reasonable accuracy. It is the length of time required to collect the required number of patients (which can be estimated if the annual intake is known) plus the length of time until the result of the treatment is evaluated.

In contrast to the sequential methods, valid evaluation of the results is only possible once the entire trial has been completed. This constitutes an advantage in as much as it keeps the administration of the trial simple. It has the disadvantage that a statistically justified conclusion is difficult to draw if an interim comparison of survival rates shows that the results differ greatly. The sequential methods lead automatically to a rapid decision in such situations.

With the χ^2 test one is only justified in discontinuing the trial when the number of deaths under one treatment (A) is already so much larger than that under the other method (B) that even when the results still to come would be as favourable as possible for A, the conclusion would still have to be that B was significantly better than A. Naturally, such a situation will only occur rarely. It is only possible once the results are known for the vast majority of patients included in the trial.

TABLE S1. *The requisite number of patients for each of the two therapies according to the χ^2 test for a 2×2 table (two-sided test; level of significance: $\alpha = 5\%$; minimum power: $100 - \beta = 95\%$)**

Probability of success after B (in %)	Probability of success after A (in %)										
	0	10	20	30	40	50	60	70	80	90	100
0		63	31	20	14	11					
10	63		323	98	50	31	21	15	11		
20	31	323		483	133	63	37	24	16	11	
30	20	98	483		589	154	70	39	24	15	
40	14	50	133	589		642	161	70	37	21	
50	11	31	63	154	642		642	154	63	31	11
60		21	37	70	161	642		589	133	40	14
70		15	24	39	70	154	589		483	98	20
80		11	16	24	37	63	133	483		323	31
90			11	15	21	31	50	98	323		63
100						11	14	20	31	63	

* Based on an article by Paulson (1947), but adjusted to 2-sided testing (cf. Appendix Part VI).

TABLE S2. *The requisite number of patients for each of the two therapies according to the χ^2 test for a 2 × 2 table (two-sided test; level of significance: $\alpha = 5\%$; minimum power: $100 - \beta = 90\%$). Figures obtained by multiplying the numbers of table S1 by 0.809 (cf. Appendix Part VI, pag. 184).*

Probability of success after B (in %)	Probability of success after A (in %)										
	0	10	20	30	40	50	60	70	80	90	100
0		51	25	16	11	9					
10	51		261	79	40	25	17	12	9		
20	25	261		391	108	51	30	19	13	9	
30	16	79	391		477	125	57	32	19	12	
40	11	40	108	477		519	130	57	30	17	
50	9	25	51	125	519		519	125	51	25	9
60		17	30	57	130	519		477	108	40	11
70		12	19	32	57	125	477		391	79	16
80		9	13	19	30	51	108	391		261	25
90			9	12	17	25	40	79	261		51
100						9	11	16	25	51	

§ 4. *Wilcoxon's test for two samples*

Wilcoxon's test is a statistical method which uses survival time since commencement of treatment as the criterion of the results. It leads to the conclusion that therapy A is better than therapy B when the patients treated by method A survive for significantly longer after commencement of treatment than those treated by method B. A high intake of patients per unit of time is favorable because it reduces the starting-up period of the trial to a minimum.

For calculating the numbers of patients required for the Wilcoxon test, we must not only specify the difference in result we want to demonstrate, as in the χ^2 test, but we must also specify the survival curve after the two methods of treatment. For a more detailed discussion of Wilcoxon's test the reader is referred to Part VI of the Appendix.

§ 5. *Sequential Analysis*

A different possibility is represented by the sequential methods analysis. For one of the sequential techniques considered, patients are divided into pairs. This may be done by constantly forming pairs of two successively admitted patients. It is, however, preferable if possible to pair every patient with another patient who resembles her in certain characteristics important to the result of treatment. This may mean that a pair of patients can only be completed after some time.

Therapy A is then assigned to one member of each pair and therapy B to the other, always at random; lots must be drawn as soon as the first patient of the pair starts treatment (cf. Appendix Part VI).

§ 6. *The constitution of homogeneous groups*

All diseases, in our case mammary carcinoma, have their natural course. There are many possible variations in biological characteristics such as rate of growth, hormone-dependence, sex chromatin and the manner and rate of metastatic growth. The influence which these characteristics exert on the course of the disease is insufficiently known, if at all. Instituting a therapy means that a characteristic is added to the natural course, with the intention of influencing it favorably. The influence of this added characteristic on the course can be evaluated only in its relation to as many as possible of the natural characteristics considered capable of influencing the course. If the individual characteristics of the patients are not taken into account, the same therapy can be expected to yield considerably different results.

If a trial is limited exclusively to patients possessing those characteristics that will be influenced precisely by the methods of treatment to be studied, a maximal effect may be expected from this trial. Accordingly, strict criteria will have to be defined to be fulfilled by the patient and the tumor before the patient can be included in the trial; the criteria must be adequate for the investigation to be carried out.

These criteria must be defined in such a way that no doubt is possible concerning their interpretation. Thus homogeneous groups of patients are formed which allow of specific analysis. Only then will it be possible accurately to determine in what way and to what degree the therapy has affected the course of the disease. It will be obvious, for instance, that when a local treatment with a curative intention is to be evaluated, no patients will be included in the trial whose pathological process has already spread beyond the area to be treated. This reasoning does not imply that a trial with a heterogeneous patient material is impossible.

If we were to include all available patients into a trial intended to evaluate the effect of a certain therapy on the local process, the treatment would have little or no influence on the evolution of the disease in a considerable number because the pathological process would already have spread beyond the area to be treated. This renders analysis of the trial very difficult and it is even doubtful whether valid conclusions could be reached at all. Owing to the inclusion of a group of irrelevant patients, a possible favorable effect of a therapy might well not manifest itself clearly. As appears from the design of numerous current trials investigators are thoroughly aware of the favorable effect of maximum homogeneity of the patient groups where the investigation in question is concerned (Flamant, 1969).

In this context Bradford Hill (1960) wrote: 'the basic principles are randomization, replication and unbiased observation. In a simple experiment in the laboratory the scientific worker wishes to see what happens to A if he manipulates B. He tries to keep constant all other factors that may upset or influence the relationship. Similarly in the controlled trial we endeavour to keep constant the characteristics of our patients that may influence the comparisons of those on treatment A and those on treatment B. Some of those characteristics we can keep constant by stratification – by keeping equal in the two groups such obvious features as age and sex. Other characteristics we cannot deliberately equalize, and our aim is to achieve it by the random allocation which, in in the long run, offers no favour to one or other group'.

As argued above, it is important for homogeneous groups to be formed from the patient material. These groups are selected on the basis of factors able to influence the result of a treatment, e.g. clinical stage, patient's age, localization of tumor, etc.

The possibility may then be taken into account that two methods of treatment are equivalent for one group but not for another. The number of patients available per group must be as large as possible in order that the statistical test applied may have sufficient power. Let us suppose that in view of the desired power per method of treatment, S patients are required per group when two therapies (t) are compared and both are applied to the same number of patients, *the number of patients actually included in the trial* e.g. the statistically required minimum number

$$X_{\text{clinical trial}}\ (X_{ct}) = t \times S = 2S.$$

Suppose the group concerned consists of F of the total number of patients who suffer from the disease.

The total number of patients with mammary carcinoma that must be available if the trial is to be possible X_{material} (X_m) must now fulfil

$$\frac{F}{100} \times X_m \geqslant t \times S$$

or

$$X_m \geqslant \frac{100}{F} \times t \times S$$

The least number of patients X_m required in order for a justified conclusion still to be possible in the subgroup is then

$$(1) \qquad X_m = \frac{100}{F} \times t \times S$$

in which F is the percentage corresponding to the subgroup to be examined and t the number of therapies compared.

In order to facilitate the calculation of X_m we have introduced the multiplication-factor $\frac{100}{\%} = \frac{100}{F}$.

If the subgroup concerned makes F% of the material available, $\frac{100}{F}$ *indicates the factor by which the number of patients required on statistical grounds (S) must be multiplied if all patients included in the trial are to meet the criteria.*

Conversely we can deduce from equation (1) the relative size $F_{\text{min.}}$ of the smallest subgroup within which the methods of treatment can still be compared if the total number n of patients available is known. This number must be substituted for X_m in (1) and F solved:

$$(2) \qquad F_{\text{min.}} = \frac{100 \times t \times S}{n}$$

Accordingly when planning a clinical trial we must know the number of patients who are or will become available, but we must also know how these patients are divided between the relevant subgroups. In practice it is often impossible to obtain exact data

on these points. Every reasonably reliable, if general, information on this point is of importance, however. At first we only need to know the order of magnitude of the number of patients required to decide whether a particular clinical trial will be feasible or not with the available patient material. If in the course of the experiment it appears that the required number of patients is not reached in certain subgroups, we can always decide to continue the experiment longer or refrain from drawing conclusions where these subgroups are concerned. We must also consider the calculations carried out in this thesis. On the basis of the available material of mammary carcinoma in The Netherlands we have attempted to deduce the percentages of subgroups of interest for comparing therapies. We are aware that these patients do not constitute a sample from a well-defined patient material obtained according to recognized techniques of random selection. Nevertheless, we consider the sample sufficiently representative of the population of Dutch women suffering from mammary carcinoma to substitute the percentages calculated from this group into one of our equations (1) and (2) so as to obtain an impression of the size of an adequate clinical trial concerning mammary carcinoma.

Possibly superfluously, we would point out in this connection that this does not run counter to our decision not to use the data for a retrospective comparison. Even though it is a reasonable assumption that the clinics involved will not have applied any radical selection in accepting patients with mammary carcinoma for treatment (or at any rate none other than is usually applied in this respect), this does not guarantee that no selection was applied in selection of treatment. And such a guarantee would be necessary for a retrospective comparison of therapies.

Still, our calculations are only orientative in character. Even if the patient material had been a random sample from the population of mammary carcinoma patients in The Netherlands during the period of the trial, we still have to take into account the normal random sample variation in the percentages calculated as well as the fact that the composition of the population may change with the passage of time. In regard to the random sample variation, suppose a particular percentage is estimated as F% and the total material contains n patients. The relative error in the percentage found and accordingly in the minimum number of patients required according to equation (1), will, with a margin of error of 5 to 10% (F not too near 0 or 100%) not exceed

$$2\sqrt{\frac{100 - F}{nF}}$$

From this we can conclude that if for n = 1,417 patients for the subgroup, we estimate a percentage of 10 on the basis of the random sample variation, we may expect a relative error exceeding 16% in the calculated number of patients required for a clinical trial. This relative error is listed for different values of F and n = 1,417 in table S3.

This table shows that the relative errors which may occur do not necessarily constitute an objection since it is only our intention to make a general estimate of the number of patients required. It should, however, be remembered that other (systematic) errors may also play a part in the estimation of percentages of patients in the various subgroups, since our material is not necessarily representative of all characteristics.

TABLE S3. *Table of two times the relative standard error e in the required number of patients as a function of the selection percentage F. The sampling error will usually not exceed e.*

F (%)	e (%)
5	23 2
10	15 9
15	12 6
20	10 6
25	9 2
30	8 1
35	7 2
40	6.5
45	5 9
50	5 3
55	4 8
60	4 3
65	3 9
70	3 5
75	3 1
80	2 7
85	2 2
90	1 8
95	1 3

The factors which may affect the treatment of mammary carcinoma are e.g. special characteristics of the tumor or of the patient, such as the extension of the pathological process expressed as the stage according to one of the international standard classifications, the site of the tumor, the age of the patient and her curative operability. Two of these characteristics, the stage classification (§ 8) and the curative operability (§ 7) are discussed later in greater detail.

In order to determine their influence on the number of patients required for a clinical trial for this purpose, the characteristics determining the natural course of the disease must first be listed. It will thus be found that in an average series of patients some characteristics are very frequent while others occur more sporadically. Particularly when we combine sporadic characteristics, this combination will occur only rarely.

In order to show how to calculate the percentage of a subgroup selected on the basis of various criteria, we give a concrete example. Suppose these criteria imply that the patients concerned have a stage I tumor at an age under 70 years, with a tumor with lateral localization which in retrospect might be regarded as suitable for curative surgery. In that case the percentage F of the patients in this subgroup may be calculated by means of the following equation:

$$(3) \qquad \frac{F_n}{100} = \frac{f_1}{100} \times \frac{f_2}{100} \times \frac{f_3}{100} \times \frac{f_O^*}{100}$$

In this equation:

f_1 = the percentage of patients available with a stage I tumor

f_2 = the percentage of patients available with a tumor in stage I and aged under 70 years

* The symbol O is used here to indicate the curative operability.

f_3 = the percentage of patients available under 70 with stage I tumors with a lateral localization, and

f_O = the percentage of patients available under 70 with laterally localized tumors in stage I, who in retrospect were found to have been suitable for curative operation.

In this formulation, the possibility is left open that the various factors by which the patients are subdivided depend on each other. The percentages f_2, f_3 and f_O do not stand in relation to the entire group of available patients who have the properties mentioned in the categories above. If instead we substitute percentages of the entire group of patients into equation (3), it must be assumed that the factors in the various categories are independent. If independence is assumed, use can be made of the data for the calculation of F from the single tables (f1 — f50, cf. Appendix Part I).

However, it is possible that two characteristics to be considered in the study are dependent (e.g. age and menopause). In that case F can be computed only if the combined frequency (f_c) of two characteristics is known. Should this dependence be neglected, then the number of patients will be over- or underestimated. When two characteristics are dependent, use must be made of the contingency tables and the combined frequency f_c must replace the product of the individual frequencies.

The contingency tables have been worked out for 15 characteristics in an attempt to gain an impression of the influence of eventual dependencies on our computation. Elaboration of the combined frequencies between other, less frequent characteristics seemed less meaningful, because our calculation only aims at a global estimate.

No combinations of more than two characteristics have been worked out in the f_c tables. On page 55, however, we present an example in which F is calculated from our f_c tables. In addition we show the result of the same calculation carried out by computer, in which all possible dependencies have been taken into account. In this example the ultimate outcomes are highly similar.

If a parallel examination of different subgroups is desired, we must calculate the number X_m on the basis of the frequency F of the smallest subgroup. However, this has the consequence that more patients possessing the less rare characteristics will be available than are strictly necessary for the trial.

It will be clear from the above that the more we select in the two therapy groups, the greater the total number of patients required (X_m) will become, because this number depends on the percentage of incidence of the select group in the patient material. As table S1 shows, the number of patients S required depends not only on differences in the 'success' percentages in the population but also on their average values. If this lies close to nil or 100%, the required number S grows smaller for the same difference. In this connection we may attempt to apply such a selection that a large difference may appear in 'success percentages', which means we want a subgroup of patients in which it may be expected that one of the two methods of treatment compared will be specifically more suitable than the other, while at the same time in the selection of the success criteria we strive for a high, or conversely, a low, mean percentage of success in the two groups (for a detailed calculation cf. Ch. V §2 p. 65).

However, the problem here lies in the fact that as soon as there are grounds for expecting a considerable difference in success percentages, the ethical permissibility of the trial becomes doubtful. Presumably the best we may expect from a selection in subgroups is that somewhere a large, unexpected difference in success percentages will occur, with relatively high or relatively low percentages of success.

This chapter deals with the attempt to get an idea of the numbers of patients suitable for inclusion in the material to be studied after completion of a clinical trial. One of the factors that may influence this number is the curative operability. We regard as curatively operable those patients who in principle might be cured completely by means of a particular therapy. Patients in whom the pathological process has already spread outside the region to be treated are regarded as curatively inoperable. When we intend to study in principle curative local treatments, we only can use real stage I or stage II patients. When afterwards it appears that a number of these patients must be classified as stage IV, this group of patients must be excluded from the trial. In the headings of the tables concerning curative operability (cf. Appendix Part II), we shall use the letter O.

Patients dying of causes other than tumor must also be excluded from the trial. Even if we wish to exclude all patients with a double carcinoma or with carcinoma other than a mammary carcinoma, the precise number of these patients can only be determined after the end of the trial, unless it is decided to exclude only those patients that fulfil this condition at the beginning of the trial. One of the data that can only be known after the trial is the number of patients who for some reason cannot be followed up until the end of the trial.

If it is found in retrospect that a number of patients have been classified incorrectly, and consequently have been included incorrectly in the trial, it is permissible to exclude these patients from the trial if the phenomenon can be expected to an equal extent in the two groups to be compared.

In calculating the number of patients necessary, it is desirable to take this factor into account if the number of patients concerned are considerable. Owing to coincidence, the distribution over the patient groups may show great differences. However, the groups remain comparable in spite of this difference, because they were composed by lots, and statistical analysis remains possible although the optimal fifty-fifty division is now lost.

The success of a clinical trial may depend on the inclusion or exclusion of the curatively inoperable patients. The presence of a large number of patients whose prognosis cannot be expected to be influenced by the treatment may render the ultimate differences in the results so small that the superiority of any form of treatment can no longer be determined.

This problem will be particularly in evidence with local therapies, aimed at the curative treatment of the local process, and less clearly with general therapies that may influence the time of appearance of distant metastases (e.g. ovariectomy cf. clinical trial Paterson Ch. V § 3, or treatment with cytostatic agents).

If only the effects of general therapies on the frequency of local and regional recurrence are to be studied, irrespective of the development of distant metastases, it is better not to select cases on the basis of curative operability.

The consequences of the 'curative operability' for a clinical trial are as follows: Given a population of patients in whom the effect of treatment A is to be compared with that of treatment B, it is to be expected that for a part of this population, to be estab-

lished beforehand or in retrospect, the effect of both methods of treatment will be the same (mostly nil). These patients we shall call the irrelevant cases (irrelevant as regards the methods of treatment to be compared) or 'curatively inoperable' patients.

The presence of irrelevant patients in a clinical trial may exert an unfavorable influence on the discriminative qualities of the tests to be applied, so that the number of patients necessary may be relatively larger than when the irrelevant patients are left out of the trial. Both the effect on the difference in result and the effect on the number of patients necessary will be demonstrated by the following example.

If we assume that two therapies A and B are compared in a clinical trial with patients in stage I, II and III, then the patients who die within 3 years after the beginning of the therapy are regarded as irrelevant. On the basis of the data listed in table O 8, we expect that this will be the case in 40 % of the patients. Therefore, if we commence the test by applying therapies A and B in equal groups of patients, both of which have been composed at random, the chance that a person will prove to be irrelevant is 40 % in both groups. Now let us assume that the irrelevant patients are not included. This means that our therapy groups actually consist of patients who are still alive at least 3 years after the beginning of the therapy and that we evaluate the result of the trial on the basis of the numbers of these patients who are dead 7 years later. Let us further assume that the 10 year mortality chances are 60% and 70%, and the 3 year mortality chance in both groups, 40%. The chance that a patient will survive for longer than 3 years but for shorter than 10 years then amounts in group A to $60 - 40 = 20\%$ and in group B to $70 - 40 = 30\%$. In relation to the group of the relevant patients ($100 - 40 = 60\%$ of all patients), therefore, there is a 10 year mortality chance of $20/60 = 33.3\%$ in group A, and of $30/60 = 50\%$ in group B; this difference in mortality chance of 16.7% in the relevant patients is equivalent to the difference between 60 and 70% in all patients. Now let us assume that the irrelevant patients are counted in. In both therapy groups we include 589 patients. According to table S1, there will then be a 95% chance that a significant difference between the therapies will be found, when the 10 year mortality chances P_A and P_B are 60% and 70%, respectively.

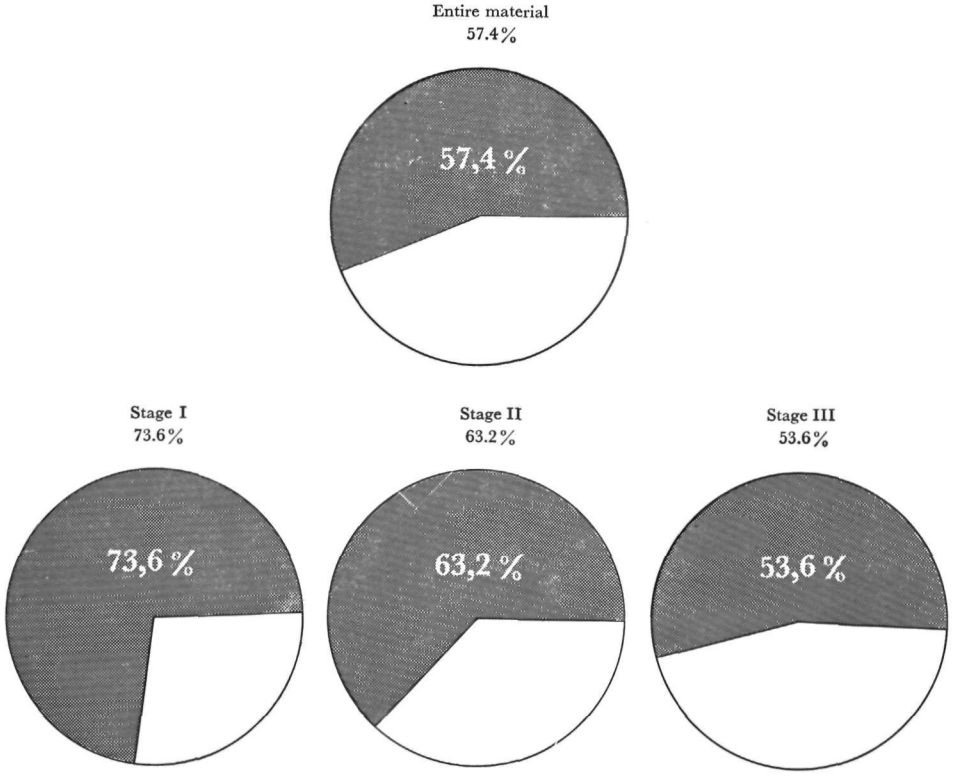
Now if the irrelevant patients are left out and $P_A = 33.3\%$ and $P_B = 50\%$, we find that per therapy 154* patients are necessary for these differences to be demonstrable; predictably, therefore, per therapy group $\frac{100}{60} \cdot 154 = 256$ patients in all. This is only 43.5 % of the 589 patients who are thought to be necessary when the irrelevant patients are not concerned beforehand. Accordingly, exclusion of the irrelevant patients in this case means a considerable decrease in the number of patients necessary for a particular difference in the 10 year mortality rate to be demonstrable.

Why the curative operability is considered as important

A study of the figures in our material concerning the course of the disease raised the question of the validity of an evaluation of the results of therapies intended as curative

* In view of the construction of table S1, a value of 30% has been chosen for P_A and value of 50% for P_B.

FIGURE III-1. *The 'curative operability' on the basis of 'death from tumor within 3 years after the beginning of the treatment' (10 years follow up, cf. Appendix table O4); each clinical stage considered as 100%.*



in a group of this kind. A considerable number of patients with stage I, II or III tumors showed obvious distant metastases shortly after institution of treatment (cf. tables O1–O2), and many patients died shortly after (cf. tables O5–O6, figures III-1 and III-4). It seems highly likely that the distant metastases were already present in these patients when treatment was started. It is unlikely that in these cases the course can have been influenced by a therapy meant only to cure the local and regional disease process.

Moeys (1953) wrote in this context: 'When a cancerous growth has been removed in toto and no metastases have been found during the operation, the conclusion that the patient has been cured is unfortunately unjustified. Cancer is not a local abnormality but a systemic disease. To my mind, a mammary carcinoma has already produced disseminations outside the field of operation of even the most radical surgeon'.

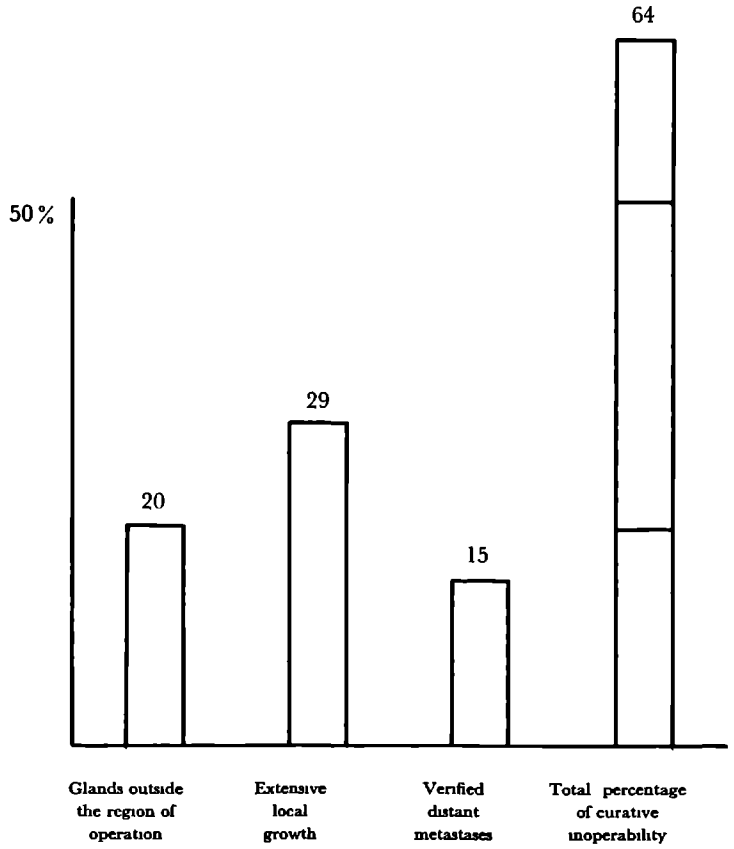
McDonald (1958) and McWhirter (1955) have also presented arguments in favor of a limited curative operability. On the basis of data from the literature, McDonald (1958) presented a study of mammary carcinoma according to their biological character. He studied groups of untreated and treated patients and concluded that therapy

cannot influence an unfavourable course in 40% of patients with mammary carcinoma; in another 40% the course is favourable and likewise uninfluenced by therapy. In only 20% of patients can early effective therapy be expected to influence the disease process.

If our multiplication factor (cf. Ch. III §6) regarding the operability was computed on the basis of the number of patients suitable for an attempt to establish the value of therapy in mammary carcinoma, then according to McDonald, the multiplication factor would amount to $\frac{100}{\%} = \frac{100}{20} = 5$.

McWhirter (1955) likewise made an estimate of the percentage of inoperable patients on the basis of data from the literature. He did so in view of the rate of occurrence of pathological glands in the various glandular regions, the local dissemination and distant metastases. Pathological axillary glands were found in 34% of cases; of this group, 60% showed supraclavicular or parasternal metastases. These patients can be considered as curatively inoperable.

FIGURE III-2. *Specification of the inoperable patients according to McWhirter*



This gives us (cf. Figure III-2):

Glands outside the region of operation	20%
Extensive local growth	29%
Verified distant metastases	15%
Total percentage of curative inoperability	64%

The remaining 'curative operability' is therefore 36%. Using these data, our multiplication factor would amount to $\frac{100}{\%} = \frac{100}{36} = 2.8$ according to McWhirter.

In a recent article by Bruce et al. (1970) we have found additional arguments in favor of our views on curative operability. On the basis of the patterns of recurrent disease in 876 patients, 65% of which had been treated according to the method of McWhirter (follow up 10 years or more), the authors conclude 'Our experience has made it abundantly clear that distant recurrence is the essential feature of therapeutic failure, and, when there is both local and distant recrudescence, the local and the remote lesions are virtually synchronous'. Stages I and II (Manchester classification) were regarded as 'potentially curable'. Local recurrence is encountered in 31% of this group of patients and distant metastases in 49% (cf. table III-1 and table III-2).

TABLE III-1. *Local recurrence in 'potentially curable' patients**

Clinical stage	No. of patients	Site of local recurrence			No. of patients with local recurrence	% incidence of local recurrence
		Axilla	Chest wall	Supraclavicular		
I	238	33 (14%)	35 (15%)	26 (11%)	58	24
II	185	54 (29%)	48 (26%)	33 (18%)	73	40
'Potentially curable'	423	87 (21%)	83 (20%)	59 (14%)	131	31

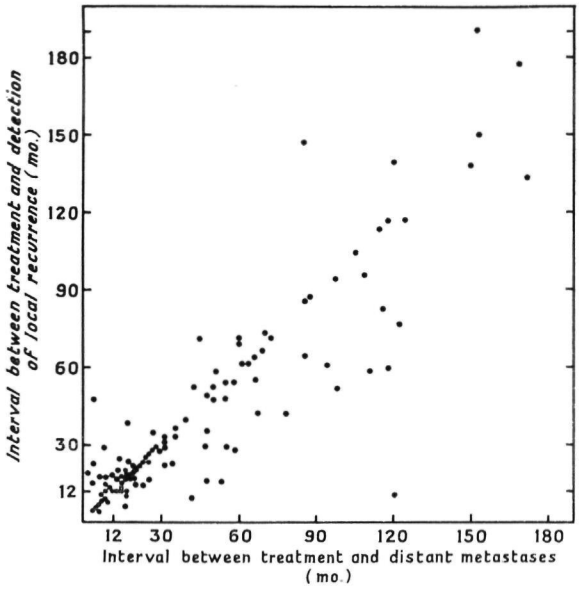
TABLE III-2. *Distant metastases in 'potentially curable' patients**

Clinical stage	No. of patients	No. with distant metastases	No. with skeletal metastases	% incidence of distant metastases
I	238	104	60	44
II	185	104	55	56
Potentially curable'	423	208	115	49

It further appears from this study that the largest number of recurrences are seen during the first 3 years after the beginning of the treatment (cf. Figure III-3 from Bruce).

* Table from Bruce (1970).

FIGURE III-3. *Time-intervals between primary treatment and the detection of recurrent disease in 112 potentially curable patients showing evidence of local and distant recurrence (from Bruce, 1970).*



The degree of 'curative operability' of mammary carcinoma was also estimated on the basis of data from our own material. A patient was regarded as 'curatively inoperable' by the author when occult distant metastases were present at onset of treatment. Two criteria were applied in this estimate, viz:

1. Manifestation of distant metastases within 3 years of starting treatment.
2. Death as a result of tumor growth within 3 years of starting treatment.

According to this assessment the remaining part of the series was regarded as 'curatively operable'. For computation we must define a period within which metastases must be demonstrable to warrant a conclusion of curative inoperability. However, since the rate of metastatic growth is uncertain, such a definition is impossible. Nevertheless, in order to gain an impression of the rate of metastatic growth and related 'curative operability', we computed for both criteria the figures over a 3 year period from starting treatment. The 3 year period was chosen because our material indicates that some 40% of distant metastases become manifest within 3 years and some 40% of the patients of our series died of tumor within 3 years.

An additional argument in favor of a term of 3 years as a criterium of the curative operability is the length of time that elapses between the first occurrence of distant metastases and the time of death of the patients in our series. The duration of this period gives an impression of the growth rate of metastases. In order to demonstrate this, an analysis was made of data concerning the 357 patients who were followed up for 10 years; no stage-classification was made. The metastases were classified according

All diseases, in our case mammary carcinoma, have their natural course. There are many possible variations in biological characteristics such as rate of growth, hormone-dependence, sex chromatin and the manner and rate of metastatic growth. The influence which these characteristics exert on the course of the disease is insufficiently known, if at all. Instituting a therapy means that a characteristic is added to the natural course, with the intention of influencing it favorably. The influence of this added characteristic on the course can be evaluated only in its relation to as many as possible of the natural characteristics considered capable of influencing the course. If the individual characteristics of the patients are not taken into account, the same therapy can be expected to yield considerably different results.

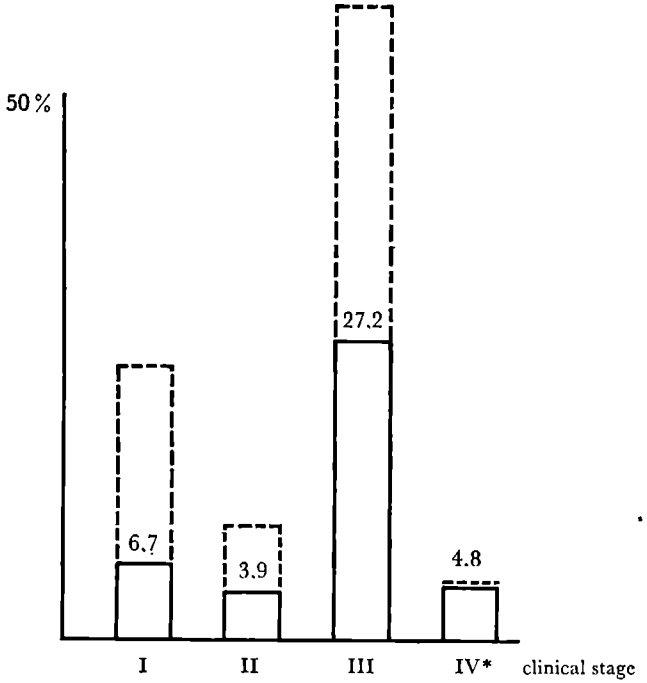
If a trial is limited exclusively to patients possessing those characteristics that will be influenced precisely by the methods of treatment to be studied, a maximal effect may be expected from this trial. Accordingly, strict criteria will have to be defined to be fulfilled by the patient and the tumor before the patient can be included in the trial; the criteria must be adequate for the investigation to be carried out.

These criteria must be defined in such a way that no doubt is possible concerning their interpretation. Thus homogeneous groups of patients are formed which allow of specific analysis. Only then will it be possible accurately to determine in what way and to what degree the therapy has affected the course of the disease. It will be obvious, for instance, that when a local treatment with a curative intention is to be evaluated, no patients will be included in the trial whose pathological process has already spread beyond the area to be treated. This reasoning does not imply that a trial with a heterogeneous patient material is impossible.

If we were to include all available patients into a trial intended to evaluate the effect of a certain therapy on the local process, the treatment would have little or no influence on the evolution of the disease in a considerable number because the pathological process would already have spread beyond the area to be treated. This renders analysis of the trial very difficult and it is even doubtful whether valid conclusions could be reached at all. Owing to the inclusion of a group of irrelevant patients, a possible favorable effect of a therapy might well not manifest itself clearly. As appears from the design of numerous current trials investigators are thoroughly aware of the favorable effect of maximum homogeneity of the patient groups where the investigation in question is concerned (Flamant, 1969).

In this context Bradford Hill (1960) wrote: 'the basic principles are randomization, replication and unbiased observation. In a simple experiment in the laboratory the scientific worker wishes to see what happens to A if he manipulates B. He tries to keep constant all other factors that may upset or influence the relationship. Similarly in the controlled trial we endeavour to keep constant the characteristics of our patients that may influence the comparisons of those on treatment A and those on treatment B. Some of those characteristics we can keep constant by stratification – by keeping equal in the two groups such obvious features as age and sex. Other characteristics we cannot deliberately equalize, and our aim is to achieve it by the random allocation which, in in the long run, offers no favour to one or other group'.

FIGURE III-4. *The number of patients (in percentages) 'died of tumor within 3 years after starting treatment' by stages (International TNM classification).*
The whole series 10 years follow up is 100 percent.
Broken lines: number of patients (in percentages) of whole series 10 years follow up, by stage.



* New manifestation of distant metastases within 3 years.

to localization, viz. local and/or regional recurrence and metastases in lungs, bones, liver, skin, brain or contralateral breast. The registration was based on one particular localization, with determination of the duration of survival after this metastasis had manifested itself, alone or in combination with metastases in some other localization. In every group of metastases, the total number of patients who exhibited metastases in that particular localization was regarded as 100%. In case of combination of two or more localizations, the course was registered for both cases. Patients with metastases in more than one localization were counted in anew for every localization.

As can be seen in table III-3 and table III-4, it is only patients with local and/or regional recurrences and patients with bone metastases who survive for longer than 3 years. This is the case only if there is no combination with other localizations.

The evolution is then as follows (cf. table III-3):

TABLE III-3. *The period that elapses between the first occurrence of local and/or regional recurrence and bone metastases respectively and the moment of death. The percentages indicate what portion of the total number of patients in each groups has died.*

Localization without combination with other metastases	total number of patients (= 100%)	% of deaths per year*					
		0	1	2	3	4 – 5	> 5
Local and/or regional	37	18 9	29 7	8 1	8 1	24 3	10 8
Bone	31	22 6	25 8	19 4	9.7	19.4	3.2

If combinations with other localizations are counted in, the course is as follows:

TABLE III-4. *The period that elapses between the first occurrence of metastases and the moment of death. In every metastatic group, all the metastases that occurred in combination with this localization were always included. The percentages indicate what portion of the total number of patients in every group of metastases has died.*

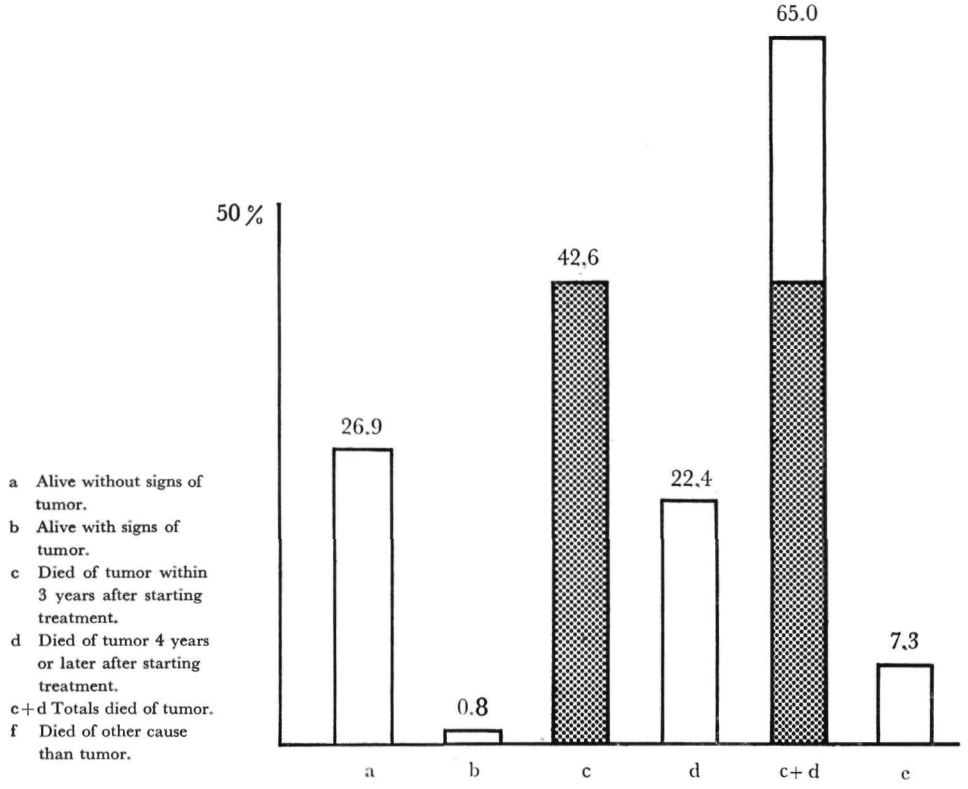
Localization	total number of patients (= 100%)	% of deaths per year*					
		0	1	2	3	4 – 5	> 5
local and/or regional	75	41 3	32 0	8 0	6 6	5 3	6 6
lungs	58	62 1	34 5	3 4	—	—	—
bone	63	48 0	32 0	12 7	4 8	1 6	1 6
liver	24	83 3	16 7	—	—	—	—
skin	8	75.0	12 5	—	12 5	—	—
brain	16	81.3	12 5	6 3	—	—	—
contralateral	7	42 9	28 6	14 3	14 3	—	—

We have arbitrarily selected a duration of 3 years as the criterium of curative operability. We are fully aware that after 3 years a manifestation of tumor growth outside the area treated may equally well indicate the presence of these metastases at the time of the treatment. Nevertheless we regard this period of 3 years as important because a development of metastases after its end rather tends to indicate a lack of radicality of the local or regional treatment, resulting in a new spread of tumor cells. However, the above considerations tend to show that the application of clinical classifications can never have more than very limited value in the definition of the prognosis. Accurate determination of the stage of clinical spread will only become possible with an improvement in the early diagnosis of distant metastasis.

The estimation of the curative operability was made from our material, which had been followed up for 5 years or more and 10 years or more. We also made a division according to clinical stages (International TNM classification): stage I through stage IV. The data concerning the curative operability are recorded in absolute figures, in percentages per stage and in percentages per combination of stages (cf. tables O 1, 2,

* The figure 0 indicates 0 – 1 year after the beginning of the treatment.
The figure 1, 1 – 2 years etc.

FIGURE III-5. *End results of treatment of mammary carcinoma. 10 years follow up. Different treatment modalities not considered, all stages included (cf. Appendix Part II table O6).*



5, 6, Appendix Part II). From these figures the multiplicationfactor was computed using table $\frac{100}{\%}$ (cf. Appendix Part IV), and recorded in table O3, 4, 7, 8 (cf. Appendix Part II).

We must point out that the different methods of treatment in our series, are not considered in the assumption that they are not essential in this respect. The number of patients required for a definite clinical trial must be multiplied by the computed multiplicationfactor (from O tables) if the percentage 'curative operability' is taken into account.

Another characteristic influencing the number of patients suitable for follow up is mortality from disease other than that under investigation. In our material the mortality from other causes was 9.0% (whole series 5 year follow up) and 7.3% (whole series 10 year follow up). This means that respectively 100–9.0 = 91% and 100–7.3 = 92.7% of the whole series have not died from other causes than tumor. The multiplicationfactors are $\frac{100}{91} = 1.10$ and $\frac{100}{92.7} = 1.08$ respectively. In our computation regarding some imaginary trials (cf. Ch. IV) this factor is accounted for on the basis of the number of patients who died from other causes within 3 years ('high risk patients' 3.5%).

'Differences in staging have more influence upon the statistical results than differences in treatment.'

McWhirter 1956.

§ 8. *Clinical classifications*

In the attempt to obtain some impression of the prognosis on the basis of the clinical symptoms, a number of clinical classifications have been introduced. In these classifications the severity of the disease is expressed by 4 stages. Stage I indicates a limited spread of the disease, and the higher stages (II, III and/or IV) a greater spread. Such classifications should make it possible, during examination and definition of the indications of treatment, to define accurately what categories of patients are considered.

In clinical trials, it is important to form groups of patients with identical characteristics, because in this way the efficacy of the various methods of treatment can be better defined (cf. Ch. III § 6).

In regard to carcinoma of the breast, numerous classifications are in use and not always with identical criteria. With the aid of such data a scheme of treatment may be devised and the value of the therapeutic schemes later analysed. The question of whether it is indeed possible and useful to draw up a classification as to prognosis on the basis of the clinical symptoms will not be considered in this chapter (for curative operability cf. Ch. III § 7).

The discussions in this chapter are helpful in demonstrating the necessity of the use of comparable groups of patients in investigations concerning carcinoma of the breast. As can be seen in table III-5, where a number of series of patients are compared that have been subdivided according to different classifications, the staging differs so much that it is unlikely that these differences are to be attributed to population differences exclusively.

TABLE III-5. *A survey of the absolute and relative numbers of patients per stage, according to several clinical classifications for mammary carcinoma (a report of the literature).*

Clinical classification	Stage I	Stage II	Stage III	Stage IV	Totals
International TNM	–	–	–	–	–
Lucassen (1964)	23 4	21 5	41 5	13 6	**100.0**
International TNM	414	183	743	69	1409
Present series	29 4	13 1	52 7	4 8	**100.0**
American TNM	549	156	375	139	1219
MacKay (1966)	45 0	12 8	30 8	11 4	**100.0**
Steinthal	147	591	183	–	921
Richards (1948)	16 0	64 0	20 0	–	**100.0**
Columbia*	216	135	48	26	425
Butcher (1961)	50 8	31.8	11 3	6 1	**100.0**
Manchester	582	481	250	569	1882
McWhirter (1955)	31 0	26 0	13 0	30 0	**100.0**

* Columbia classification stage A, B, C and D.

Not all investigators consider the differences between the classifications as important. Handley (1967) for instance regards as equivalent stage III of the International TNM Classification, stage III of the modification of the TNM system proposed by the American Joint Committee on Cancer Staging and End Results reporting of the American College of Surgeons, and stage C of the Columbia Clinical System. Zippin (1966), on the other hand, has pointed out the differences between the American TNM Classification and the International TNM Classification. His findings are listed in table III-6.

Numbers
% Horizontal
% Vertical

TABLE III-6. *International TNM classification versus American TNM classification (from Zippin 1966), modification to our tables.*

	International TNM classification				
American TNM classification	Stage IV	Stage III	Stage II	Stage I	Totals
Stage IV	*195*	*30*	—	—	*225*
	86 7	13 3			100.0
	100 0	5.0			12.7
Stage III		*381*	—	—	*381*
		100.0			100.0
		63 6			21.6
Stage II	—	*73*	*236*	—	*309*
		23 6	76.4		100.0
		12 2	100 0		17 6
Stage I	—	*115*	—	*734*	*849*
		13.5		86 5	100.0
		19 2		100 0	48 1
Totals	*195*	*599*	*236*	*734*	*1764*
	11 0	34 0	13.4	41 6	100.0
	100.0	100.0	100.0	100.0	100.0

In order to gain an impression of the degree of comparability of various classifications we compared on our own material several commonly-used classifications with the International TNM classification we used (UICC 1968). This comparison is highly artificial and gives only a general impression.* The chief problem in this respect was that the International TNM classification entirely ignores certain symptoms considered essential in another classification, e.g. 'the size of axillary glands' or 'the occurrence of carcinomatous mastitis' in the Columbia classification. Efforts were made to establish which of the TNM categories determine the stage of tumor growth in the International TNM classification. This is elucidated in a diagram. As regards other classifications, the TNM categories essential to each stage were likewise charted, always on the basis of the highest stage (legend cf. p. 36). With every diagram, the conditions of the classification in question are stated.

* For this comparison, the 8 patients whose classification was unknown were included in stage III.

The following clinical classifications are considered:

a. The Classification of the Joint Committee on Cancer Staging and End Results Reporting of the American College of Surgeons (American TNM) (Spratt 1967).
b. Steinthal Classification (Steinthal 1905).
c. Columbia Classification (Spratt 1967).
d. Manchester Classification (Windeyer 1949).

On the basis of the foregoing data we computed the stage distribution in our material in the terms of the other classifications. For this purpose a computer program was designed to determine in each classification the TNM categories corresponding with the highest stage, to count the number of patients meeting these criteria. This number was subtracted from the material. The lower stages were successively counted and subtracted from the remaining material. The figures thus obtained were used in compiling the contingency tables of the TNM classification versus each of the other classifications.

The relative frequency distribution of the various stages is shown in the following tables III-7—III-10 and Figures III-6—III-9, which reveal considerable differences. The degree of consistency of the various stages between the International TNM system and the other classifications was computed from the number of patients who came under the same stage heading in the various classifications (cf. table III-11). The diagrams clearly reveal the difference in structure of the stages, on comparison of the different classifications. Comparison of the figures from our material also reveals considerable differences. In our opinion therefore, a comparison of different methods of treatment in groups of patients who have been classified according to different systems is not very useful, and will give rise to numerous misunderstandings, to the detriment of the patients.

The International TNM classification

T — Primary tumour

T0 No evidence of primary tumour.

T1 Tumour 2 cm or less in greatest dimension;
Skin not involved, except in the case of Paget's disease confined to nipple;
No retraction of nipple;
No pectoral muscle fixation;
No chest wall fixation.

T2 Tumour more than 2 cm but not more than 5 cm in greatest dimension, *or*
incomplete skin fixation (tethered or dimpled), *or*
nipple retraction (in subareolar tumours), *or*
Paget's disease extending beyond the nipple;
No pectoral muscle fixation;
No chest wall fixation.

T3 Tumour more than 5 cm but not more than 10 cm in greatest dimension, *or*
skin fixation complete (infiltrated or ulcerated), *or*
peau d'orange in tumour area, *or*
pectoral muscle fixation[1] (incomplete or complete). No chest wall fixation.

1 Incomplete pectoral muscle fixation indicates that contraction of the muscle limits tumour mobility. Complete pectoral muscle fixation indicates that contraction of the muscle abolishes tumour mobility.

T4 Tumour more than 10 cm in greatest dimension, *or*
skin involvement *or* peau d'orange wide of tumour but not beyond breast area, *or*
chest wall fixation.[2]

2 The chest wall includes the ribs, intercostal muscles and serratus anterior muscle but not the pectoral muscle.

N — Regional lymph nodes

The clinician may record whether palpable nodes are considered to contain growth or not

N0 No palpable homolateral axillary nodes.

N1 Movable homolateral axillary nodes

N1*a* Nodes not considered to contain growth.

N1*b* Nodes considered to contain growth

N2 Homolateral axillary nodes fixed to one another or to other structures.

N3 Homolateral supra- or infra-clavicular nodes movable or fixed *or* oedema of the arm [3]

[3] Oedema of the arm may be caused by lymphatic obstruction, lymph nodes may not then be palpable.

M — Distant metastases

M0 No evidence of distant metastases.

M1 Distant metastases present

M1*a* Skin involvement wide of breast

M1*b* Involvement of contralateral nodes or contralateral breast

M1*c* Clinical or radiographic evidence of metastases to lungs, pleural cavity, skeleton, liver, etc.

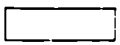
Stage-grouping

With M0, classification by T and N gives stages as follows

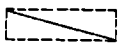
Stage I	T1N0	T2N0
Stage II	T1N1	T2N1
Stage III	T1N2	T2N2
	T1N3	T2N3
	T3N0	T4N0
	T3N1	T4N1
	T3N2	T4N2
	T3N3	T4N3

With M1 stage must be IV.

EXPLANATION OF THE DIAGRAMS



The categories which determine the same stage in both systems were boxed in with a continuous line



Categories included in the International TNM but not in the classification considered were boxed in with an interrupted line and cancelled.

The categories classified in a different stage in the classification considered were boxed in with a continuous line, boxes with an interrupted line were used to indicate where these categories were placed in the TNM system. The arrow indicates the direction of the category-displacement.

	Stage I	Stage II	Stage III	Stage IV
Size	T1	T1	T1	T1
	T2	T2	T2	T2
	T3	T3	T3	T3
	T4	T4	T4	T4
Skin	T1	T1	T1	T1
	T2	T2	T2	T2
	T3	T3	T3	T3
	T4	T4	T4	T4
Paget's disease	T1	T1	T1	T1
	T2	T2	T2	T2
Nipple retraction	T2	T2	T2	T2
Pectoral muscle attachment	T1	T1	T1	T1
	T3a	T3a	T3a	T3a
	T3b	T3b	T3b	T3b
Chest wall attachment	T1	T1	T1	T1
	T4	T4	T4	T4
Homolateral axillary lymph nodes	N0	N0	N0	N0
	N1a	N1a	N1a	N1a
	N1b	N1b	N1b	N1b
	N1x	N1x	N1x	N1x
	N1y	N1y	N1y	N1y
	N2a	N2a	N2a	N2a
	N2b	N2b	N2b	N2b
Homolateral supraclavicular or infraclavicular lymph nodes	N3	N3	N3	N3
Arm edema	N3	N3	N3	N3
Distant metastases	M0	M0	M0	M0
	M	M	M	M

* The TNM categories which determine the Stages are boxed in.

The American TNM classification, proposed by the American Joint Committee on Cancer Staging and End Results reporting of the American College of Surgeons

T: Primary Tumor

T1 Tumor of 2 cm. or less in its greatest dimension; skin not involved, or involved locally with Paget's disease

T2 Tumor over 2 cm. in size or with skin attachment (dimpling of skin) or nipple retraction (in subareolar tumors); no pectoral muscle or chest wall attachment

T3 Tumor of any size with any of the following: skin infiltration, ulceration, peau d'orange, skin edema, pectoral muscle or chest wall attachment

N: Regional Lymph Nodes

N0 No clinically palpable axillary lymph nodes (metastasis not suspected)

N1 Clinically palpable axillary lymph nodes that are not fixed (metastasis suspected)

N2 Clinically palpable homolateral axillary or infraclavicular lymph nodes that are fixed to one another or to other structures (metastasis suspected)

M: Distant Metastasis

M0 No distant metastasis

M1 Clinical and radiographic evidence of metastasis except those to homolateral axillary or infraclavicular lymph nodes

These descriptions are then combined to define four stages.

Stage I: T1/N0/M0; T2/N0/M0

Stage II: T1/N1/M0; T2/N1/M0

Stage III: T3/N0/M0; T3/N1/M0; T3/N1/M0; T3/N2/M0; T1/N2/M0; T2/N2/M0; and includes any combination of T1, T2 or T3 with N2 and M0

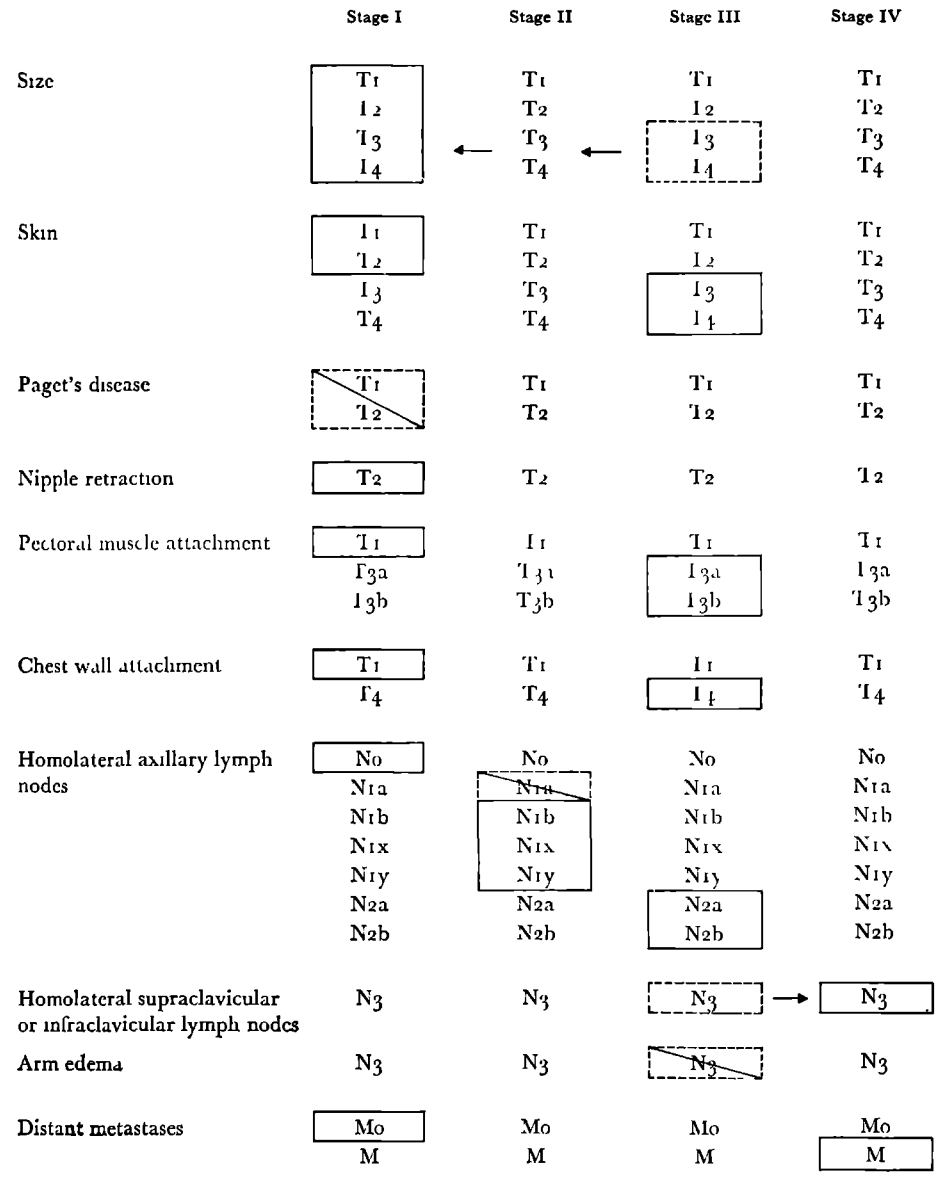
Stage IV: Any clinical stage of disease with distant metastasis (M1).

Numbers
% Horizontal
% Vertical

TABLE III-7. *American TNM classification* versus *International TNM classification.*

American TNM classification	International TNM classification				
	Stage IV	Stage III	Stage II	Stage I	Totals
Stage IV	*69*	*62*			*131*
	52.7	47.3			100.0
	100.0	8.2			9.3
Stage III		*468*	*13*		*481*
		97.3	2.7		100.0
		62.3	6.9		33.9
Stage II		*84*	*133*	*12*	*229*
		63.7	58.1	5.2	100.0
		11.1	70.8	2.9	16.1
Stage I		*138*	*42*	*396*	*576*
		24.0	7.3	68.7	100.0
		18.4	22.3	97.1	40.7
Totals	*69*	*752*	*188*	*408*	*1417*
	4.8	53.1	13.2	28.9	100.0
	100.0	100.0	100.0	100.0	100.0

The American TNM classification projected on to the International TNM classification) **)*



*) Skin edema not considered.

**) Infraclavicular lymph nodes headed under N2.

The Steinthal classification

STAGE I Cancers limited to the breast so far as can be determined by palpation and clinical study

STAGE II Cancers in which the axillary lymph nodes are palpable, and clinically suspected of harbouring neoplastic deposits
In this stage there is no evidence of implication of any other neighbouring organ or tissue

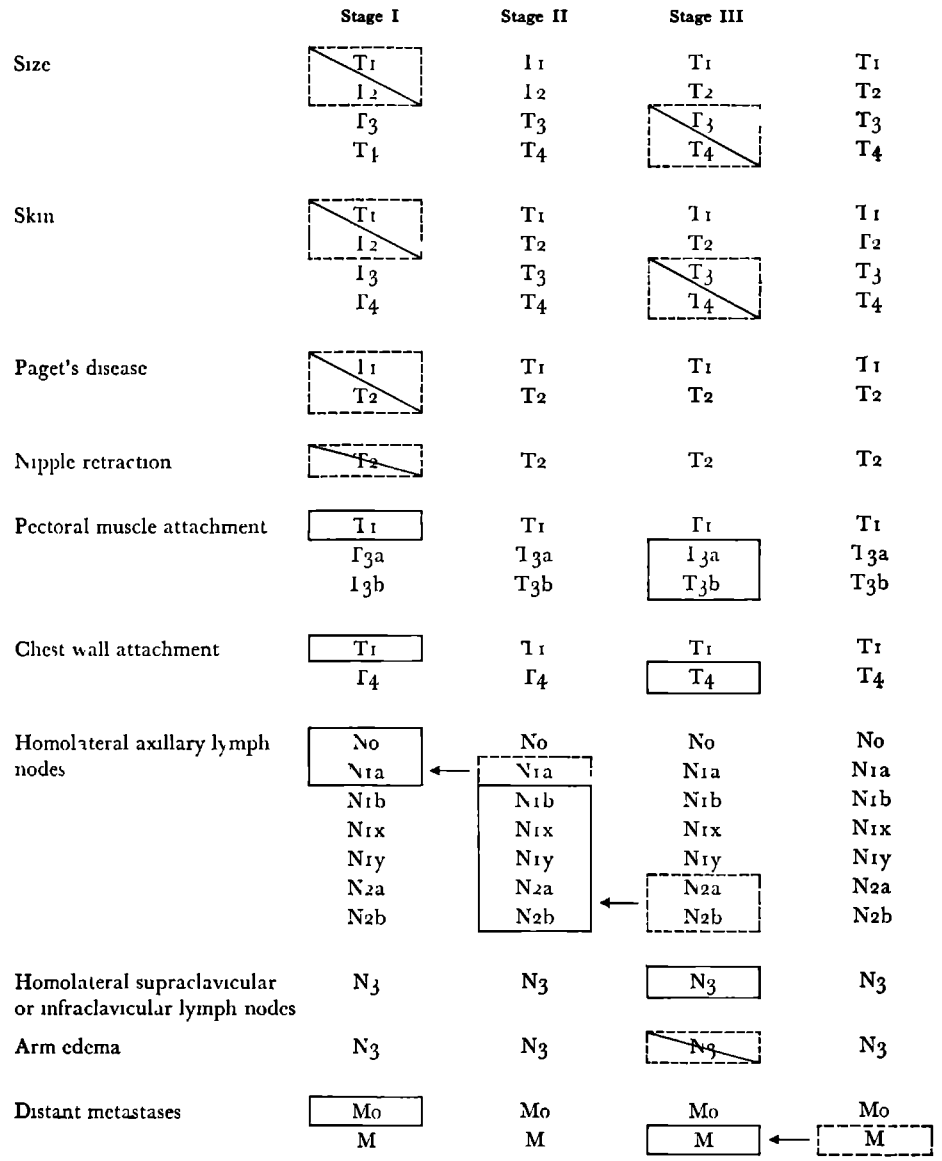
STAGE III Cancers in which adjacent organs or tissues are involved by the neoplasm e g the pectoral muscles, the skin when ulcerated, the opposite breast, cervical lymph nodes, the skeletal tissues, etc

Numbers
% Horizontal
% Vertical

TABLE III-8. *Steinthal classification* versus *International TNM classification.*

Steinthal classification	International TNM classification				
	Stage IV	Stage III	Stage II	Stage I	Totals
Stage III	*69*	*129*			*198*
	35 0	56 0			100 0
	100 0	17 1			14 0
Stage II		*270*	*145*	*9*	*424*
		63 7	34 2	2 1	100 0
		36 0	77 1	2 2	29 8
Stage I		*353*	*43*	*999*	*795*
		44 3	5 4	50 3	100.0
		46 9	22 9	97 8	56 2
Totals	*69*	*752*	*188*	*408*	*1417*
	4 8	53 1	13 2	28 9	100.0
	100.0	100 0	100.0	100.0	100.0

The Steinthal classification projected on to the International TNM classification



STAGE A: No skin edema, ulceration or solid fixation of tumor to chest wall; axillary nodes not clinically involved.

STAGE B: No skin edema, ulceration or solid fixation of tumor to chest wall, clinically involved axillary nodes, but less than 2 5 cm. in transverse diameter and not fixed to overlying skin or deeper structure of axilla.

STAGE C: Any one of five grave signs of comparatively advanced carcinoma:

1. Edema of skin of limited extent (less than one third of the skin over the breast).
2. Skin ulceration
3. Solid fixation of tumor to chest wall.
4. Massive involvement of axillary lymph nodes (2 5 cm or more in transverse diameter)
5. Fixation of the axillary nodes to overlying skin or deeper structures of the axilla.

STAGE D: All other patients with more advanced breast carcinoma including:

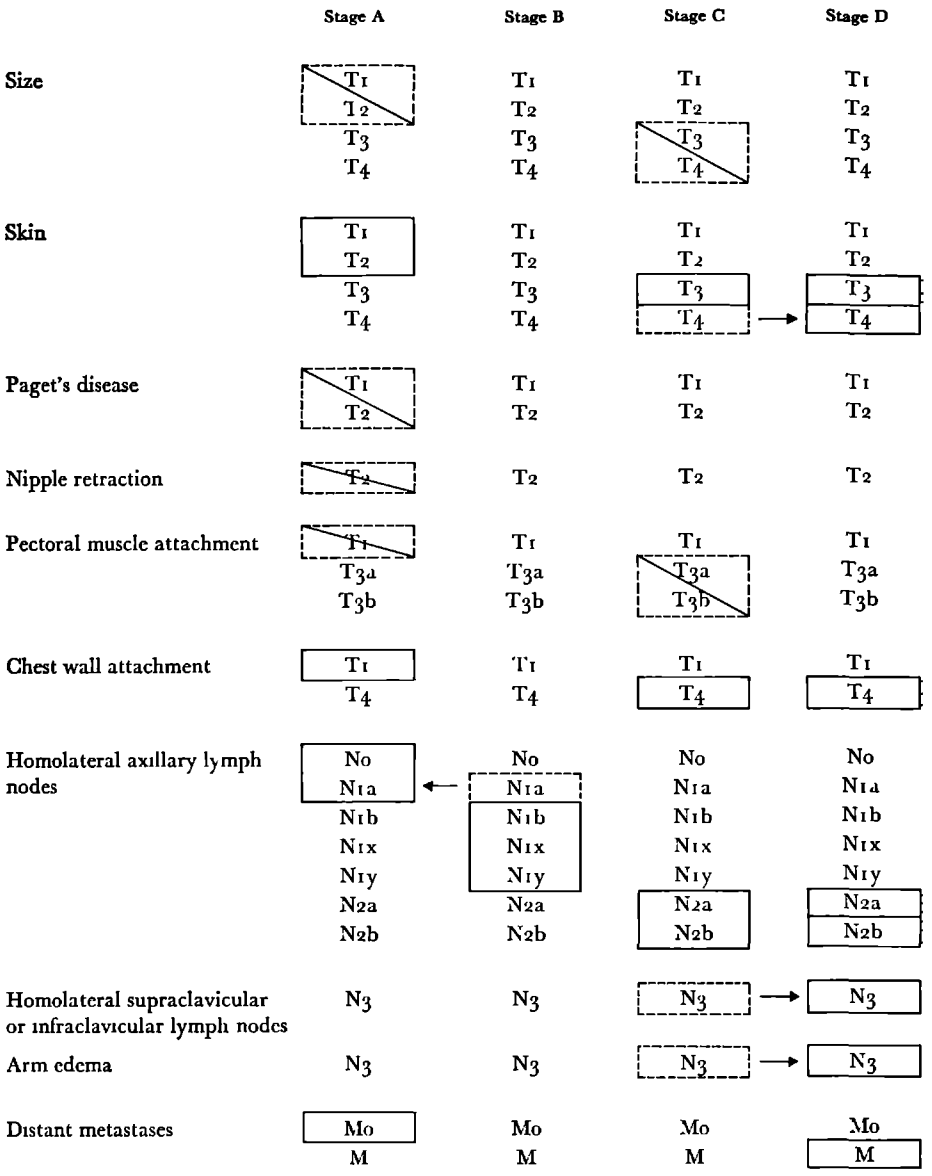
1. A combination of any two or more of the five grave signs listed in Stage C.
2. Extensive edema of skin (involving more than one third of the skin over the breast).
3. Satellite skin nodules.
4. The inflammatory type of carcinoma
5. Supraclavicular metastases, clinically
6. Parasternal metastases, clinically.
7. Edema of the ipsilateral arm.
8. Distant metastases.

Numbers
% Horizontal
% Vertical

TABLE III-9. *Columbia classification* versus *International TNM classification.*

Columbia classification	International TNM classification				
	Stage IV	Stage III	Stage II	Stage I	Totals
Stage D	*69*	*134*			*203*
	34.0	66 0			100.0
	100.0	17.8			14 3
Stage C		*295*			*295*
		100.0			100.0
		39.1			20 8
Stage B		*130*	*145*	*8*	*283*
		45.9	51.2	2.9	100.0
		17.3	77.1	2.0	20.1
Stage A		*193*	*43*	*400*	*636*
		30.4	6.7	62.9	100.0
		25.8	22.9	98.0	44 8
Totals	*69*	*752*	*188*	*408*	*1417*
	4.8	53.1	13 2	28.9	100.0
	100.0	100.0	100.0	100.0	100.0

The Columbia classification projected on to the International TNM classification *) **)*



* Where two boxed-in categories are connected with one another by a line, these categories count only where they are pre in combination.

** Size of the axillary lymph nodes, skin edema, satellite skin nodules, the inflammatory type of carcinoma, parasternal me tases (clinically), not considered.

STAGE I : The growth is confined to the breast Involvement of the skin directly over and in continuity with the tumor does not affect staging provided that the area involved is small in relation to the size of the breast.

STAGE II As Stage I but there are palpable mobile lymph nodes in the axilla.

STAGE III The growth is extending beyond the corpus mammae as shown by:

a The skin is invaded or fixed over an area large in relation to the size of the breast

b. The tumor is fixed to underlying muscle Axillary glands may or may not be palpable but if glands are present they must be mobile

STAGE IV The growth has spread beyond the breast area as shown by

a Fixation of axillary nodes indicating extension outside the capsule

b. The tumor is completely fixed to the chest wall

c Secondary lymph nodes in supraclavicular region.

d Secondary deposits in skin- wide of tumor

e. Secondary deposits in the opposite breast

f Distant metastases, e g bone, liver, lung, etc

Numbers
% Horizontal
% Vertical

TABLE III-10. *Manchester classification* versus *International TNM classification*

Manchester classification	International TNM classification				
	Stage IV	Stage III	Stage II	Stage I	Totals
Stage IV	*69*	*167*			*236*
	29 2	70 8			100.0
	100 0	22 2			16 7
Stage III		*363*	*13*		*376*
		96 5	3 5		100.0
		48 2	6 9		26 6
Stage II		*108*	*163*	*25*	*296*
		36 5	55 1	8 4	100 0
		14 4	86 7	6 1	20 9
Stage I		*114*	*12*	*383*	*509*
		22 4	2 4	75 2	100.0
		15 2	6 4	93 9	35 8
Totals	*69*	*752*	*188*	*408*	*1417*
	4 8	53 1	13 2	28 9	100.0
	100 0	100.0	100.0	100.0	100.0

The Manchester classification projected on to the International TNM classification

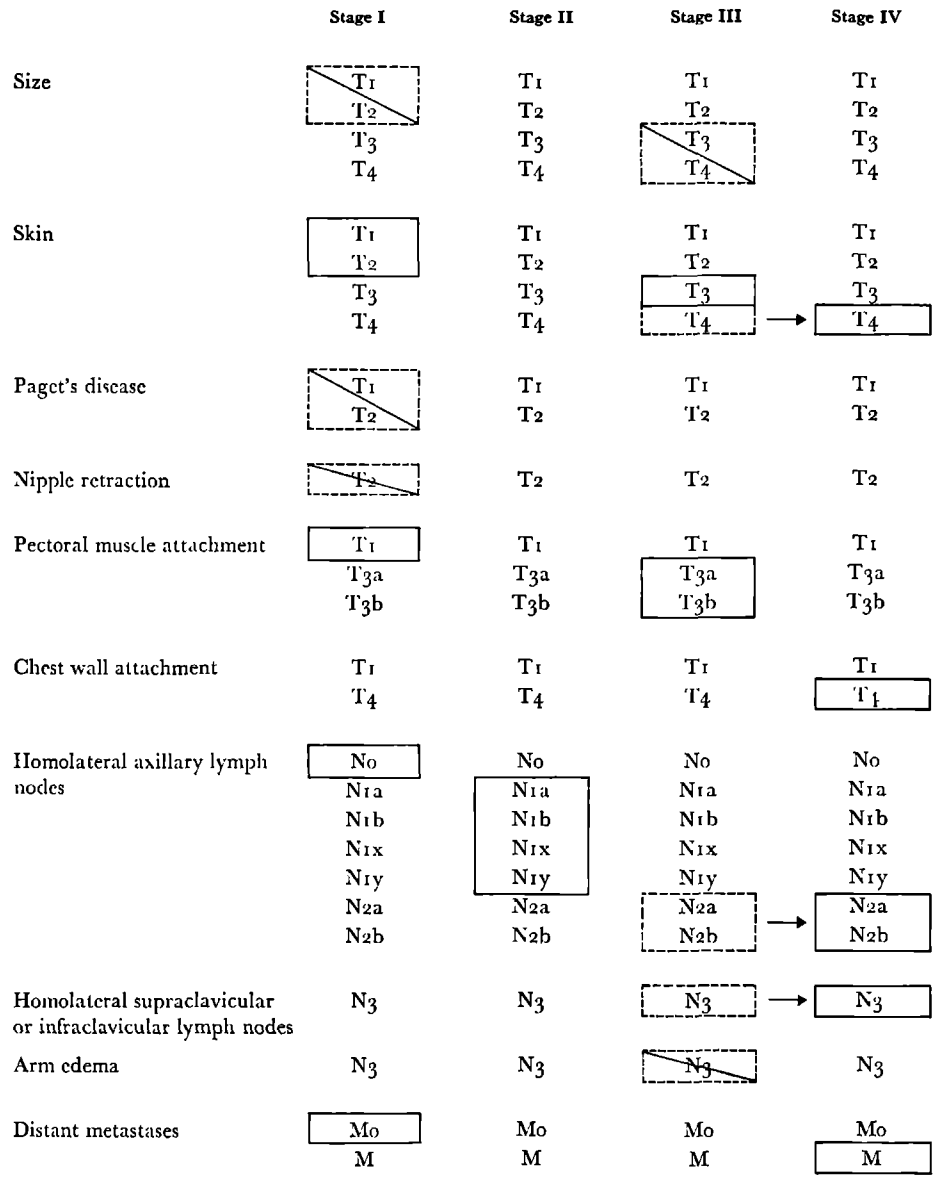


TABLE III-11. *The number of patients in the various classifications (in absolute and relative frequencies) under the same stage-heading as the International TNM Classification. (The series of 1417 patients is 100%)*

Clinical Classification	Numbers	Percentage
American TNM	1066	75.3
Steinthal	673	47.5
Columbia	909	64.1
Manchester	978	69.0

A survey of the relative numbers of patients per stage, according to several clinical classifications for mammary carcinoma (cf. tables III-7—III-10).
% Stage I (Fig. III-6) + % Stage II (Fig. III-7) + % Stage III (Fig. III-8) + % Stage IV (Fig. III-9) = 100%.

FIGURE III-6 STAGE I *(Columbia classification stage A)*

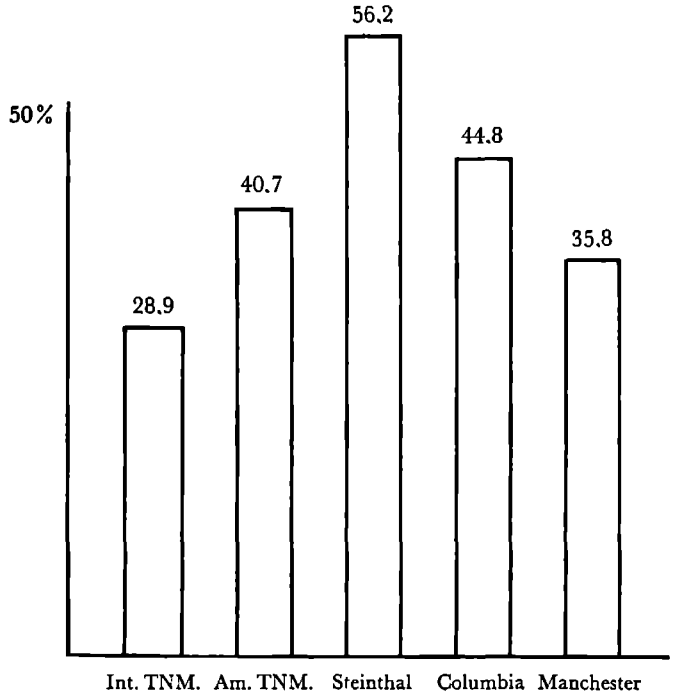


FIGURE III-7 STAGE II *(Columbia classification stage B)*

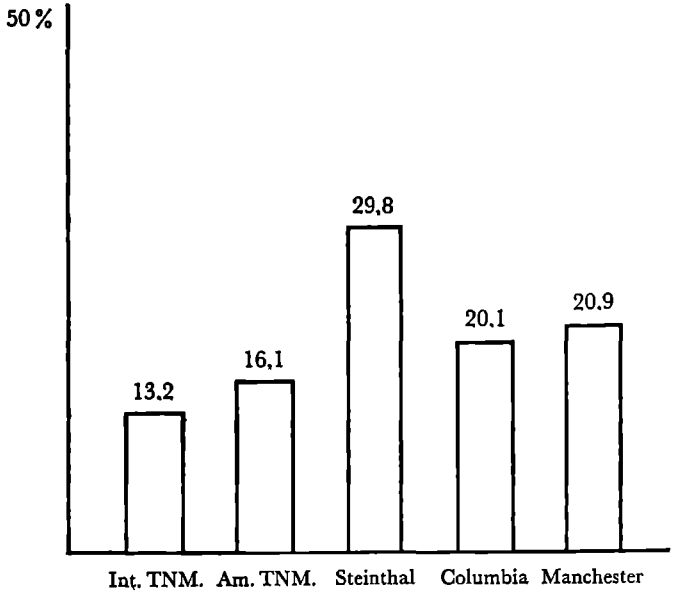


FIGURE III-8 STAGE III *(Columbia classification stage C)*

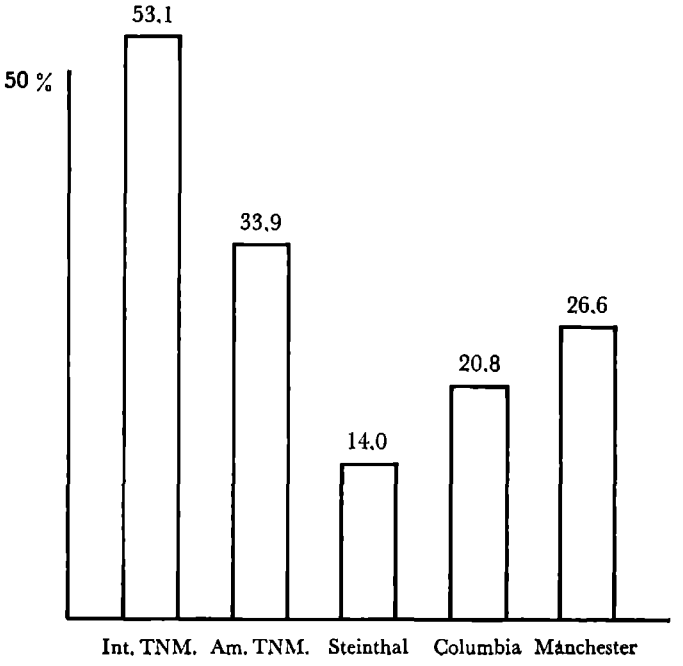
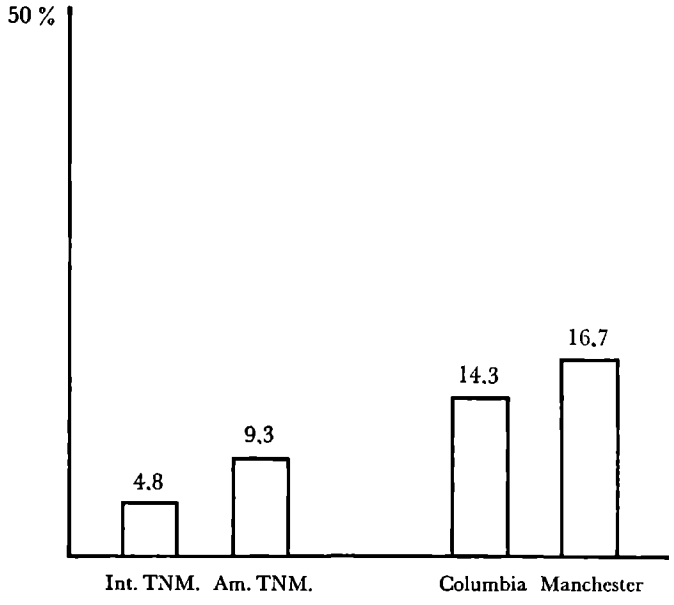


FIGURE III-9 STAGE IV *(Columbia classification stage D)*



§ 9. *The requisite number of members of the general female population*

Our computation may enable the investigator to estimate the number of patients required for a clinical trial in accordance with individual criteria. The only remaining question concerns the number of patients with mammary carcinoma available in a general population. In order to be able to calculate the size of the female population ($X_{population}$) necessary for a particular clinical trial, the multiplicationfactor $\frac{100}{P}$ has been introduced. Factor $\frac{100}{P}$ is based on the annual number of female deaths from malignant conditions of the mammary gland in the general population as recorded in tables concerning the Cancer Mortality in 24 countries (cf. table P, Appendix Part III). The assumption in using this figure is that all patients dying of mammary carcinoma are recorded, the annual mortality is not variable and the annual morbidity corresponds to the annual mortality.

The introduction of factor q, which indicates the number of years during which the patients will be included in the trial, gives an impression of the number of members of the female population who must be available per year. Our computation of X_p gives an impression of the geographical extent of the organization that is required if a clinical trial is to be carried out.

$$X_p = X_m \times \frac{(\frac{100}{P})}{q}$$

An investigator is not likely to wish to collect his entire material within one year. For the estimate, therefore, factor $\frac{100}{P}$ should be divided by the number of years (q) during which the patients are included in the trial. If the collecting period of the trial is 10 years ($q = 10$) then the required size of the female population is to be estimated with the aid of factor $\frac{\left(\frac{100}{P}\right)}{10}$

For example, if factor P is found to equal 3.3×10^3 (cf. table P, Appendix Part III) then mammary carcinoma occurs annually in 1 out of 3300 women. Computed for the 10 year period this makes $\frac{3300}{10}$ i.e. 1 patient out of 330 women. It must be remembered that it will be impossible to include all cases with mammary carcinoma in the trial. The figures supplied by the Central Cancer Registration Office in The Netherlands give an indication of the number of patients potentially available (cf. table III-12).

TABLE III-12. *The number of patients recorded by the Netherlands Central Cancer Registration (from Meinsma 1963 and 1965)*

Period	Total number of patients	Number of patients per annum
1953–1955	2181	717
1956–1958	3689	1229

An inquiry made in The Netherlands by Zwaveling (1966) has shown that far larger figures can be obtained with the collaboration of many surgeons. Zwaveling received notification of some 1494 patients per annum, i.e. the majority of some 2000 annual patients in The Netherlands.

CHAPTER IV. ESTIMATING THE NUMBER OF PATIENTS REQUIRED FOR SOME IMAGINARY CLINICAL TRIALS TO COMPARE THE RESULTS OF SEVERAL THERAPIES FOR MAMMARY CARCINOMA

In this chapter the numbers of patients required are calculated for some imaginary trials, with reference to examples. Our main intention is to give an impression with the aid of data from our patient material of the influence of progressively increased selectivity on the total number of patients required (X_m). For the number required on statistical grounds, we used table S1 of the χ^2 test for a 2×2 table. If F_n is the percentage of the entire population of patients with mammary carcinoma fulfilling n selection criteria, and f_1, f_2, f_3, etc. the percentages of incidence of every single selection criterion, F_n is calculated as follows:

$$\frac{F_n}{100} = \frac{f_1}{100} \times \frac{f_2}{100} \times \frac{f_3}{100} \text{ etc.}$$

Since the dependence, if any, is not known for all the selection factors, they are assumed to be independent in these cases. In order to gain an impression of the magnitude of error resulting from this assumption we have established with the aid of a computer how many patients in our material fulfilled all the requirements of the first trial (cf. note 6, p. 56). In order to indicate the influence of each selection factor, a new selection factor was added each time in the calculation and X_m was calculated successively. Consequently the numbers listed for a given selection factor are valid when the factors in question and/or listed previously are accepted as conditions for admission of patients to the trial. The necessary data were borrowed from the f tables (cf. Appendix)*. The required number S was always based on the condition that a difference between a probability of success $P_A = 60\%$ with treatment A and $P_B = 70\%$ with treatment B should be detectable with a probability of 95%; and for the case when $P_A = 60\%$ but $P_B = 80\%$. This condition has been selected because these figures correspond to the percentages of 5 year results in large series in the literature concerning the early stages of mammary carcinoma (cf. table IV-1). Naturally, on the basis of table S1 the calculation can also be made for other values of P_A and P_B.

* For further details concerning the calculation of X_m, cf. Ch. III § 6.

TABLE IV-1. *Results of Treatment of mammary carcinoma. Five year survival in stage A[1] patients. (Columbia Clinical Classification).*

Author	Therapy	Number of patiens	% survival
Kennedy and Miller[2]	Simple Mastectomy	115	62
Handley[3]	Modified Radical Mastectomy	117	76
Butcher[2]	Radical Mastectomy	216	76
Haagensen and Cooley[2]	Radical Mastectomy	344	84
Dahl-Iversen and Tobiassen[2]	Super-Radical	277	77
Williams and Curwen[2]	Total Mastectomy + axillary dissection + irradiation	68	72
Kaae and Johansen[2]	McWhirter's method	159	70
Baclesse[4]	Prolonged Roentgen Therapy	50	54

1 For comparability of stage A Columbia Clinical Classification and Stage I International TNM Classification cf Ch III § 8
2 Haagensen et al. 1963.
3 Handley 1965.
4 Baclesse 1965.

As mentioned previously, S may vary widely if other criteria for success of the treatment are set. In all cases, two methods of treatment were compared ($t = 2$).

The calculation then goes as follows:

$$X_m = 2S \times \frac{100}{F_n}$$

The multiplicationfactor $\frac{100}{F_n}$ (cf. table $\frac{100}{\%}$, Appendix Part IV), which indicates the factor by which the number of patients required on statistical grounds must be multiplied if all patients included in the trial are to meet the criteria set, is listed for each selection factor.

Finally we determined the minimum number of women X_p which a population must contain in order for a period of q years to yield a sufficient number of mammary carcinoma patients to permit a trial with X_m patients. Suppose P is the incidence of mammary carcinoma among the population, i.e. the number of women who develop mammary carcinoma per 100 women per year, then:

$$X_m = \frac{P}{100} \times X_p \times q \quad \text{therefore:} \quad X_p = X_m \times \frac{100}{P.q}$$

P is unknown, but we do know the number of women per 100 women per year who die from mammary carcinoma. If we assume that in nearly all women who develop this disease, the diagnosis will ultimately also be registered as the cause of death, we may

substitute for P the annual percentage mortality from mammary carcinoma in The Netherlands (cf. table P, Appendix Part III).

$$\text{When } q = 5\text{: } X_p = X_m \cdot \frac{(3.3 \times 10^3)}{5}$$

$$X_p = X_m \cdot (0\,66 \times 10^3)$$

$$X_p = 660\ X_m.$$

Therefore if the 5 year survival rate is selected as the criterion, the trial will last 10 years.

For the 4 examples worked out, we have presupposed a selection based on the following criteria:

1. The patients must be females.
2. Mammary carcinoma to be verified histologically.
3. The mammary carcinoma not to be bilateral.
4. The patient not to suffer from carcinomata other than the mammary one, with the exception of cutaneous carcinoma.
5. The excision biopsy for mammary carcinoma to be performed no earlier than two weeks prior to admission to the trial.
6. The patient not to have died within 3 years of admission to the trial from any other disease than mammary carcinoma (only to be established during the trial).
7. The patient to be less than 70 years old.

Our calculation will show (cf. table IV-2) that according to our estimate only 69.5% of the patient material fulfils these conditions. One should note that the number of high-risk patients (point 6 above) cannot be known at the beginning of the trial, so that these patients have to be preliminarily included into the trial. We have not taken into account the loss of patients due to lack of follow up. In our series, this was of the order of 1%. For registration we must therefore reckon on a larger number of patients than the statistically required minimum 2S (X_{ct}, cf. p. 20).

TABLE IV-2. *Relative frequency in our material of criteria for inclusion of patients in the imaginary clinical trials considered in tables IV-3 and IV-4.*

Criteria	f_i [1]	F_i [2]	$\frac{100}{F_i}$ [3]
1 Female patients only	100%	100%	1 00
2. Tumor verified histologically	100%	100%	1 00
3. Only unilateral mammary carcinoma	97 7%	97 7%	1 02
4. No other carcinoma (except skin carcinoma) present	98 8%	96 5%	1 04
5. Excision biopsy for verification no longer than 2 weeks ago	94 4%	91 1%	1 10
6. No high risk patients [4]	96 5%	87 9%	1 14
7 Age up to 70 (cf table f16)	79 0%	69 5%	1 44
All criteria for inclusion	–	69 5%	1 44

1) f_i = relative frequency in material of criterion considered

2) $F_i = (f_i . F_{i-1})/100$ = remaining part (percentage) of material meeting criteria considered and foregoing criteria.

3) Factor for computation of X_m (cf. Appendix Part IV)

4) The value of f_i stated here is the relative frequency of patients in our material who died from other diseases within 3 years of commencement of therapy.

FIRST DESIGN (cf. table IV-3):

Since the effect to be investigated is what may be expected from therapies aimed at the local process with its regional spread, the patient material must fulfil the following conditions.

1. The tumor must be stage I on the International TNM Classification. With the aid of our data, the size of the group of patients fulfilling these conditions can be approximated as follows. Table f_c 24 shows that 337 patients in stage I were younger than 70. The total number of patients aged up to 70 years is 1110. Of these 1110 patients, 337 (or 30.4 %) were in stage I.
2. The tumor to be localized in the lateral half of the breast (46.1% cf. table f_c 64).
3. The patient may be regarded as suitable for curative surgery (78.8% cf. table O7). This means that the patient must not die from tumor growth within 3 years of beginning the treatment.

Since we cannot know at the beginning of the trial which patients will die from tumor growth within 3 years, observation of the last condition means that a number of extra patients will have to be treated, in order to leave a sufficient number at the end of the trial. This first design is based on comparison of the results of two surgical methods of treatment A and B. The design may also be used for comparing non-surgical methods of treatment. We have, however, made this selection since the conditions for this design also apply to the designs mentioned below, where the histology of the axillary glands is of importance.

SECOND DESIGN (cf. table IV-3):

In patients who fulfil the conditions mentioned above and who have been submitted to some form of surgical treatment, we now make a distinction between histological positivity and negativity of the axillary glands (37.0% cf. table f_c 98). The group of patients with histologically positive axillary glands is divided at random into two equal groups: one group treated by X-ray and a control group. Since randomization is applied to the surgical therapy as well, any possible systematic effect of the nature of the surgical treatment is excluded. If a group of patients were available for this trial who had been treated by a uniform surgical method, more homogeneous groups might be formed which would be very favorable for demonstrating a possible systematic effect of the radiological treatment.

THIRD DESIGN (cf. table IV-3):

With a clinical trial according to this design we can study the value of prophylactic ovariectomy in non-menopausal women. For this purpose, subdivision according to menopause is made in a group of patients who fulfil the conditions of the first design. Since ovariectomy may be expected to have some influence on the development of distant metastases, the condition of 'curative operability' (78.8% of Stage I patients cf. table O7) was not applied to this design, so that the ultimate numbers of the first design must be multiplied by $\frac{78.8}{100}$. The group of non-menopausal women was divided at random into equal ovariectomy and control groups. In order to exclude any systematic effect of previous surgery and/or radiotherapy, randomization was

applied to the previous treatment as well. Of this design, as of the second design, it would be more favorable if patients were available for this trial who had previously been subjected to uniform surgical and radiological therapy.

With the aid of our data, the size of the group of patients fulfilling the conditions for non-menopausal women under 70 in stage I can be approximated as follows.

The total number of patients in stage I is 413 (cf. table f_c 24). According to table f_c 56, 27.6% of all patients in stage I are not menopausal; 27.6% of the total of 413 patients is 114. Table f_c 24 shows that 337 patients in stage I were younger than 70. Of these 337 patients, 114 (or 33.8%) were non-menopausal.

TABLE IV-3. *Estimation of number of patients required for an imaginary clinical trial in order to compare two therapies A and B.*

It is assumed that a difference of x-year population survival rates P_A and P_B has to be detected with a probability of 95% by the χ^2 test for a 2 × 2 table (at the 5% level of significance) applied on observed x-year survival rates. The value of x can be chosen arbitrarily (greater than 3 for all trials where the curative operability is taken into account). It is assumed that all patients have to meet of criteria 1–7 of table IV-2; for each trial some additional conditions (connected to the types of therapies considered) are imposed subsequently. Mutual dependencies between these conditions are not taken into account, except for those mentioned in the tables. The values of P_A and P_B may depend on these conditions, but the computation is always carried out for the same two cases $P_A = 60\%$, $P_B = 80\%$ and $P_A = 60\%$, $P_B = 70\%$.

Conditions				Case $P_A = 60\%$ $P_B = 80\%$ $2S = 266$		Case $P_A = 60\%$ $P_B = 70\%$ $2S = 1178$	
	f_i [1]	F_i [2]	$\frac{100}{F_i}$ [3]	X_m [4]	X_p [5] (millions)	X_m [4]	X_p [5] (millions)
Trial I for comparing two surgical therapies A and B							
1. All criteria of table IV-2	–	69.5%	1.44	383	0.25	1,700	1.1
2. Tumor of stage I (International TNM classification) in patients aged up to 70 years	30.4%	21.1%	4.74	1,260	0.83	5,580	3.7
3. Curative operable patients, in patients with tumor of stage I (5 years less follow up)	78.8%	16.6%	6.02	1,600	1.1	7,090	4.7
4. Tumor localized laterally, in patients with tumor of stage I	46.1%	7.65%[6]	13.1	3,480	2.3	15,400	10.
Trial II for comparing patients treated by radiotherapy (A) to a control group (B)							
1. All conditions of trial I	–	7.65%	13.1	3,480	2.3	15,400	10.
2. Patients with positive axillary glands in patients with tumor of stage I	37.0%	2.83%	35.3	9,390	6.2	41,600	27.
Trial III for comparing patients subjected to ovariectomy (A) to a control group (B)							
1. All conditions of trial I except for curative operability (condition 3)	–	9.73%	10.3	2,730	1.8	12,100	8.
2. Non-menopausal patients in patients of stage I	33.8%	3.29%	30.4	8,100	5.3	35,800	24.

1) f_i = relative frequency in our material of patients with the condition considered (percentage).

2) $F_i = (f_i . F_{i-1})/100$ = remaining part of material after imposing condition considered.

3) $100/F_i$ = factor with which the number 2S has to be multiplied in order to obtain X_m.

4) X_m = estimated number of patients required for a trial if they have to meet the condition considered and the preceding ones (to 3 significant figures).

5) X_p = estimated size of female population in which X_m patients are expected per year; $X_p = 660\, X_m$ is stated in millions (to 2 significant figures).

6) This percentage calculated directly from the number of patients fulfilling all conditions 1 through 4 in our data and the total number of patients involved (not assuming independence of conditions cf p. 51) was 7.40.

FOURTH DESIGN (cf. table IV-4):

The purpose of this trial design was to study in one series of patients the value of two methods of surgical treatment A and B combined with radiological treatment and ovariectomy. The aim was not solely to determine the effect of surgical therapy A or B and of postoperative irradiation or ovariectomy by themselves, but to gain an impression of the effect of these methods of treatment when applied to the same patient. In this respect, this design differs from earlier ones which were aimed at evaluation of one therapy only and the nature of previous therapies was not taken into account. In order to exclude a systematic effect of previous therapies, the randomization of the previous designs was applied to these therapies as well.

For this fourth design (parts II and III) use was made of more homogeneous groups of patients, since the effect of previous treatments is part of the investigation. An objection to this design is, however, that for part II (radiological treatment) and part III (ovariectomy), larger numbers of patients are required than for analogous trials as described under the second and third designs.

The fourth design consists of three parts (cf. Figure IV-1).

PART I: The patient material fulfilling the conditions of the first design is divided at random into two equal groups. One group is treated by surgical therapy A, the other by therapy B. Accordingly, part I of the fourth design is identical to the first design (cf. p. 54).

PART II: Surgical therapy groups A and B are both subdivided into groups with histologically positive axillary glands (P) and groups with histologically negative axillary glands (N). We thus have groups AP, AN, BP and BN. Groups AP and BP are once more divided at random into equal groups, of which only one group is irradiated (irradiation, APR and BPR; irradiation controls APC and BPC). Patients with histologically negative axillary glands (AN and BN) are not submitted to additional treatment.

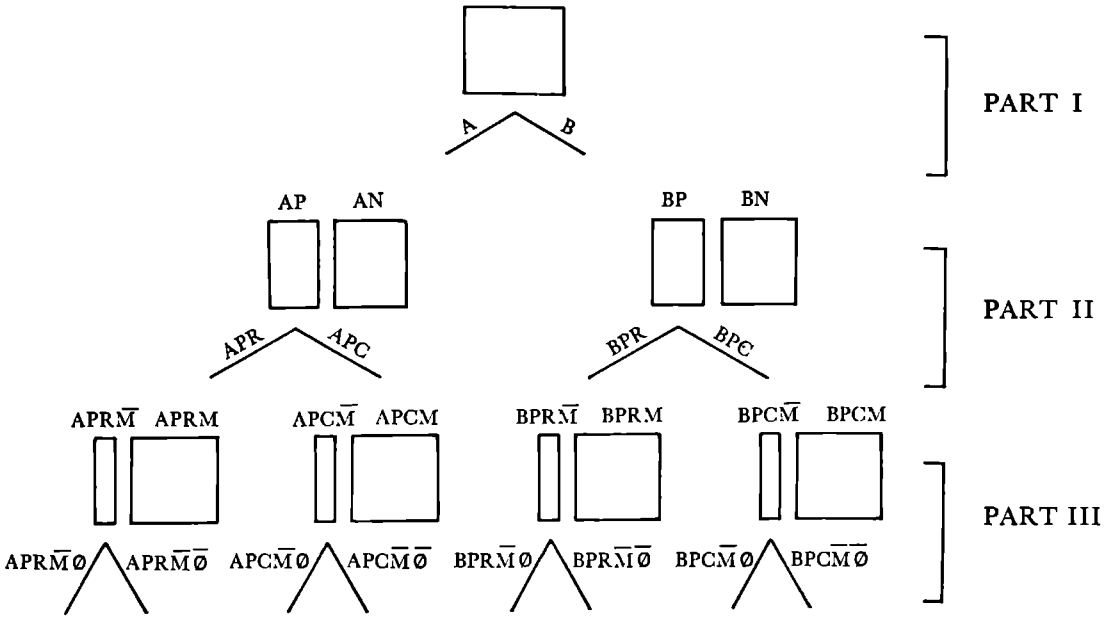
PART III: The irradiation and irradiation control groups are divided into menopausal patients (M) and non-menopausal patients ($\bar{M}$). Thus the following groups of patients are formed: APRM, APR$\bar{M}$, BPRM, BPR$\bar{M}$, APCM, APC$\bar{M}$, BPCM and BPC$\bar{M}$. The groups of non-menopausal patients in whom the presence of positive axillary glands was established during the examination for part II are now divided at random, dependent on the menopausal condition, into two equal groups of which one is subjected to ovariectomy (Ø) while the other serves as control ($\bar{Ø}$)*.

Thus, the following therapy groups are formed:

APR$\bar{M}$Ø, APR$\bar{M}\bar{Ø}$, APC$\bar{M}$Ø, APC$\bar{M}\bar{Ø}$
BPR$\bar{M}$Ø, BPR$\bar{M}\bar{Ø}$, BPC$\bar{M}$Ø, BPC$\bar{M}\bar{Ø}$.

* If in the comparison of ovariectomy groups the curative operability is not to be taken into account, the numbers found must be divided by $\frac{100}{78.8}$, or multiplied by $\frac{78.8}{100}$, as in the third design (cf. page 54).

FIGURE IV-1. *Schematic presentation of the fourth design (cf. p. 57).*



The groups of menopausal patients APRM, BPRM, APCM and BPCM are given no further treatment. If desired, part III might be extended to study the effect of irradiation in patients with negative axillary glands, groups AN and BN. In this case, therapy groups ANR, ANC, BNR and BNC would be formed. If desired, the non-menopausal patients in these groups might be subjected to a study of the effect of ovariectomy, in accordance with part III. However, the inclusion of patients with histologically negative axillary glands in the trial is of little importance for the calculation of the required number of patients X_m, since X_m is computed on the basis of the least frequent characteristic, i.e. histologically positive axillary glands. If X_m includes a sufficiently large number of patients with histologically positive axillary glands, there will undoubtedly be enough patients with histologically negative axillary glands.

TABLE IV-4. *Estimation of number of patients required for an imaginary clinical trial for comparing results of different types of therapies simultaneously.*

PART I · Both groups of patients for a trial to compare two surgical therapies (cf table IV-3, trial I) are divided into a Radiation group and a Radiation Control group
PART II · The total number of patients meeting the additional conditions of trial II (cf table IV-3) required for testing the effect of radiotherapy within each of the surgery groups is estimated.
PART III: Each of the four groups of Part II are divided into an Ovariectomy group and an Ovariectomy Control group The total number of patients meeting the additional conditions of trial III (cf table IV-3) required for testing the effect of ovariectomy within each of the four groups is estimated For assumptions and key, cf table IV-3.

Conditions	Case $P_A = 60\%$ $P_B = 80\%$ $2S = 266$					Case $P_A = 60\%$ $P_B = 70\%$ $2S = 1178$	
	f_1	F_1	$\frac{100}{F_1}$	X_m	X_p (millions)	X_m	X_p (millions)
Part I Comparing two surgical therapies A and B							
All conditions of trial I, table IV-3	–	7 65%	13 1	3,480	2 3	15,400	10
Part II Testing effect of radiotherapy within each surgery group							
Number of patients required for part I multiplied by 2 [1]	–	3 57%	26 2	6,970	4 6	30,900	20
Patients with positive axillary glands in patients with tumor of stage I	37 0%[3]	1 42%	70 4	18,700	12	82,900	55
Part III Testing effect of ovariectomy within each of the four groups of part II							
Number of patients required for part II multiplied by 2 [2]	–	0 71%	141	37,500	25	166,000	110
Non menopausal patients in patients of stage I	33 8%[3]	0 24%	417	111,000	73	490,000	320

1) For division into Radiation and Radiation Control groups
2) For division into Ovariectomy and Ovariectomy Control groups
The numbers $100/F_1$, X_m and X_p may differ slightly from twice the foregoing values since all results are rounded off after computation
3) Cf First and second designs respectively

CHAPTER V. OUR APPROACH APPLIED TO A NUMBER OF CLINICAL TRIALS FROM THE LITERATURE

§ 1. *Introduction*

In this chapter, our approach is applied to the data of some previously completed clinical trials. For this purpose we selected the studies of Kaae (1965, 1968), Paterson (1959a, 1959b, 1962) and Nissen-Meyer (1965, 1968). Clinical evaluation of the results of these trials lies outside the scope of this study.

We estimated the number of patients required for trials, assuming that the estimated population result rates were approximately the same as those actually found experimentally. This was done for differences between the population result rates from 10% up to the minimum difference detectable with a probability of 95% with the same number of patients as that considered in the trial. We based our estimates on the actual selection percentages found by the investigators and not on those in our material. These percentages were calculated from the number of patients possessing some (combined) characteristics and the total number of patients available, so no assumptions of independence of characteristics had to be made. None of the investigators mentioned took the factor 'curative operability' (cf. Ch. III §7) into account, so the required numbers of patients estimated in accordance with our approach are not corrected for curative operability. We will thus demonstrate with a few examples the extent to which tabulation of the curative operability influences the numbers of patients required. In our tables on these investigators, we first give a survey of their results. In this respect the following data are tabulated:

I Total number of patients included in trial.

II Absolute numbers and percentages of patients meeting requirements laid down by investigator.

III An indication of the therapies compared and the absolute number of patients to whom these therapies were allocated.

IV The result rates found in each of the treatment groups 5, 7 or 10 years after treatment.

V The result of the statistical test for the difference of these result rates.
If not recorded by the author, the p-value of the χ^2 test for a 2×2 table, with Yates correction, is given.

We then give our approach to the minimal detectable difference in population survival rates, obtainable from the number of patients in the trial under consideration.

VI From the percentage F of the entire series meeting the requirements (cf. II) the multiplication factor $2 \times \frac{100}{F}$ is computed (cf. IX).

VII Different values of the population survival rates P_A and P_B are chosen, approximating to the (sample) result rates actually found. The values P_A and P_B are always multiples of 10%, so that table S1 can be used.

VIII From table S1 we find the number S (the number of patients required in each therapy group to detect the difference between P_A and P_B with a probability of 95%).

IX Applying the multiplication factor to S, the total number of patients $X_m = S \times 2 \times \frac{100}{F}$ required according to our criteria is found (cf. Ch. III §6).

Operations VI–IX are carried out for differences 10%, 20%, etc. between P_A and P_B until the number X_m exceeds the number of patients actually included in the trial. In this way, the order of magnitude of the minimal detectable difference is obtained.

§ 2. *Kaae's Clinical Trial*

The clinical trial carried out by Kaae and Johansen (1965, 1968) compared two random series:

a. simple mastectomy with postoperative irradiation (McWhirter group), and

b. extended radical mastectomy by the Dahl-Iversen method. This operation is a classical radical mastectomy, extended by the inclusion of dissection of the supraclavicular and internal mammary lymph nodes. The internal mammary chain is removed from the first to fourth intercostal spaces. No supplementary irradiation was administered.

The study covered the period 1951-1957, comprising 331 cases (operable and inoperable) in the McWhirter group and 335 in the extended radical mastectomy group. Staging was partly done in accordance with the International Clinical Classification (Copeland 1959–'60) and partly according to the criteria of Haagensen (1943). The 5 year results were known for all cases, and the 10 year results were known for 234 and 250 cases respectively. A subdivision is made into stage I cases and operable minus stage I cases.

The age distribution was approximately the same in both groups, so no correction was applied in analysis. The results were analysed as crude survival rates, crude recurrence-free survival rates without correction for death, without signs of recurrence and manifestation of distant metastases. In our considerations, the figures for crude survival rates are used. In table Kaae IV the influence of the use of different criteria on the number of patients required is evaluated. Not all the patients with operable cancer admitted into the trial received the treatment scheduled for their group.

The McWhirter technique was carried out on only 76%. No operation was performed in 14% of cases on account of biological inoperability (advanced age, concomitant disease) or refusal of treatment. The remaining 10% of patients wished to be treated at other hospitals. Similarly, in the extended radical mastectomy group, all operable cases should have had extended radical mastectomy. 76% were admitted to this operation, which was carried out in all but 25 cases or 12% of the 206 patients. Fifteen proved technically inoperable at operation, and 8 were in too poor a condition for extended radical mastectomy and 2 refused to have extended radical mastectomy. They were given simple mastectomy, in some cases with partial excision of the lymph nodes and postoperative X-ray irradiation. 13% were not operated on because of biological inoperability and 1% refused. Again, 10% of the patients desired treatment at other hospitals.

TABLE KAAE I. *McWhirter's method and Extended radical mastectomy compared in operable patients, 5 and 10 years crude survival rates considered. No division into subgroups.*

			5 years follow up		10 years follow up	
I	Numbers of patients included in KAAE'S clinical trial		666 100%		666 100%	
II	Numbers of patients meeting requirements	Only "operable" patients considered. Exceptions: Biologically inoperable Refused operation Other exceptions	Operable 425 63.8%		Operable 302 45.3%	
	Clinical classification		Stage not considered		Stage not considered	
	Therapies considered		McWhirter's method	Extended radical mastectomy	McWhirter's method	Extended radical mastectomy
III	Numbers of patients per therapy group		219	206	149	153
IV	Results of percentages (crude survival rate)		66%	67%	46%	49%
V	Statistical significance (not recorded by KAAE) X^2 test: p value		p = 0.94		p = 0.72	
	Numbers of patients required according to our criteria					
VI	Percentage of entire series meeting the requirements		63.8%		45.3%	
	Multiplicationfactor	$2 \times \frac{100}{F}$	$2 \times \frac{100}{63.8} = 3.1$		$2 \times \frac{100}{45.3} = 4.4$	
	If a 10% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		P_A = 60% P_B = 70%		P_A = 40% P_B = 50%	
VIII	Number of S (cf table S_1)		589		642	
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	3.1 × 589 = 1,800 ±		4.4 × 642 = 2,800 ±	
	If a 20% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		P_A = 60% P_B = 80%		P_A = 40% P_B = 60%	
VIII	Number of S (cf table S_1)		133		161	
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	3.1 × 133 = 400 ±		4.4 × 161 = 700 ±	

P_A and P_B indicate the assumed population survival rates from McWhirter's method and Extended radical mastectomy respectively.

TABLE KAAE II. *McWhirter's method and Extended radical mastectomy compared (5 years crude survival rate). Operable patients divided into Clinical Stage I and Operable minus Stage I cases.*

		5 years follow up			
I	Numbers of patients included in KAAE'S clinical trial	666 100%			
II	Numbers of patients meeting requirements Only "operable" patients considered. Exceptions: Biologically inoperable Refused operation Other exceptions	Operable 425 63.8%			
	Clinical classification	Clinical stage I 290 43.5%		Operable minus stage I 135 20.3%	
	Therapies considered	McWhirter's method	Extended radical mastectomy	McWhirter's method	Extended radical mastectomy
III	Numbers of patients per therapy group	149	141	70	65
IV	Results in percentages (crude survival rate)	75%	77%	46%	48%
V	Statistical significance (not recorded by KAAE) X^2 test : p value	p = 0.78		p = 0.96	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	43.5%		20.3%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{43.5} = 4.6$		$2 \times \frac{100}{20.3} = 9.9$	
	If a 10% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 70% P_B = 80%		P_A = 40% P_B = 50%	
VIII	Number of S (cf. table S_1)	483		642	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	4.6 × 483 = 2,200 ±		9.9 × 642 = 6,400 ±	
	If a 20% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 60% P_B = 80%		P_A = 40% P_B = 60%	
VIII	Number of S (cf. table S_1)	133		161	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	4.6 × 133 = 600 ±		9.9 × 161 = 1,600 ±	
	If a 30% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	— —		P_A = 30% P_B = 60%	
VIII	Number of S (cf. table S_1)	—		70	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	—		9.9 × 70 = 700 ±	

P_A and P_B indicate the assumed population survival rates from McWhirter's method and Extended radical mastectomy respectively.

TABLE KAAE III. *McWhirter's method and Extended radical mastectomy compared (10 years crude survival rate). Operable patients divided into Clinical Stage I and Operable minus Stage I cases.*

			10 years follow up			
I	Numbers of patients included in KAAE'S clinical trial		666 100%			
II	Numbers of patients meeting requirements	Only "operable" patients considered Exceptions· Biologically inoperable Refused operation Other exceptions	Operable 302 45 3%			
	Clinical classification		Clinical stage I 202 30 3%		Operable minus stage I 100 15 0%	
	Therapies considered		McWhirter's method	Extended radical mastectomy	McWhirter's method	Extended radical mastectomy
III	Numbers of patients per therapy group		97	105	52	48
IV	Results in percentages (crude survival rate)		54%	58%	28%	29%
V	Statistical significance (not recorded by KAAE) X^2 test · p value		p = 0 62		p = 1	
	Numbers of patients required according to our criteria					
VI	Percentage of entire series meeting the requirements		30 3%		15 0%	
	Multiplicationfactor	$2 \times \frac{100}{F}$	$2 \times \frac{100}{30\ 3} = 6\ 6$		$2 \times \frac{100}{15\ 0} = 13\ 3$	
	If a 10% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		P_A = 50% P_B = 60%		P_A = 20% P_B = 30%	
VIII	Number of S (cf table S_1)		642		483	
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	6 6 × 642 = 4,200 ±		13 3 × 483 = 6,400 ±	
	If a 20% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		P_A = 50% P_B = 70%		P_A = 20% P_B = 40%	
VIII	Number of S (cf table S_1)		154		133	
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	6 6 × 154 = 1,000 ±		13 3 × 133 = 1,800 ±	
	If a 30% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		P_A = 40% P_B = 70%		P_A = 10% P_B = 40%	
VIII	Number of S (cf table S_1)		70		50	
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	6 6 × 70 = 450 ±		13 3 × 50 = 650 ±	

P_A and P_B indicate the assumed population survival rates from McWhirter's method and Extended radical mastectomy respectively.

In Kaae's trial, no difference in probability of survival could be demonstrated between McWhirter's method and extended radical mastectomy. This does not justify the conclusion that the two surgical methods are equivalent. The number of patients who could be followed up for 5 years was large enough according to our calculations to demonstrate a 20% difference in probability of survival with 95% probability. From this it may be concluded that if there is a difference between the chances of survival between the two methods, it is probably less than 20%. The possibility remains, therefore, that there is a difference of less than 20% between the chances of survival, but Kaae does not demonstrate this.

Similar considerations apply to the group of patients followed up for 10 years. The number of these patients, on the other hand, was only large enough to demonstrate a difference of 30% in the survival chances with 95% probability. It is therefore possible that there is a difference of less than 30% between the two chances of survival. Consequently, if it is believed possible that the chances of survival are not the same but differ by less than 20% and 30% respectively, Kaae's trial should be repeated with more patients in order that these differences may be demonstrated with reasonable certainty.

It should be noted that a repetition of Kaae's trial would give rise to problems in collecting an identical group of patients, since the composition of Kaae's material was not entirely clear because he applied two different clinical classifications to his group (cf. p. 62). From tables Kaae I, II and III we can deduce how many patients would be required to demonstrate maximum differences of 10% in survival chances. Although Kaae's publications contain no data useful in the calculation of our factor of 'curative operability', we consider it interesting to give an impression of the influence this factor may exert on the number of patients required for the design of a trial as organized by Kaae. Let us therefore suppose that the group of patients examined by Kaae and the patients classified by us at stage I + II have similar characteristics. The 'curative operability' would then amount to 70.5% (cf. table O8) and the multiplicationfactor would increase by $\frac{100}{70.5} = 1.42$.

It is to be expected, however, that the percentages of results will be closer to 0% or 100% than the percentages of results found by Kaae and that for this reason the number S will grow smaller, so that fewer, rather than more patients will be required (cf. Ch. III § 7, p. 25).

From our study it is clear that the requisite number of patients depends amongst other things on the criteria chosen in marking the results (cf. Ch. III § 3 p. 14). As an example, an attempt is made to demonstrate this on the basis of Kaae's trial. From Kaae's results we calculated the numbers of patients required according to various criteria. Kaae's table IV shows the consequences of applying different criteria of success most clearly in the group of 'operable cases' in which for the demonstration of a difference in results of 10% with a probability of 95%, for the criteria 'crude survival rate' and 'distant metastases', a total of 1,800 patients was found, whereas for the criterion 'local/regional recurrence' only 1,000 patients are sufficient.

TABLE KAAE IV. *Requisite number of patients according to different criteria of succes (5 years follow up). Operable cases, Clinical Stage I and Operable minus Stage I patients considered.*

	Operable cases, cf Kaae I			Clinical stage I, cf Kaae II			Operable minus stage I, cf Kaae II		
Criteria (5 years follow-up)	Crude survival rate cf. table Kaae I	Local/ regional recurrence	Distant metastases	Crude urvival rate cf table Kaae II	Local/ regional recurrence	Distant metastases	Crude survival rate cf table Kaae II	Local/ regional recurrence	Distant metastases
McWhirter's method[1])	66%	18%	38%	75%	15%	28%	46%	26%	59%
Extended radical mastectomy[1])	67%	22%	37%	77%	16%	27%	48%	37%	58%
Results of treatment P_A and P_B assumed[2])	$P_A = 60\%$ $P_B = 70\%$	$P_A = 10\%$ $P_B = 20\%$	$P_A = 40\%$ $P_B = 30\%$	$P_A = 70\%$ $P_B = 80\%$	$P_A = 10\%$ $P_B = 20\%$	$P_A = 30\%$ $P_B = 20\%$	$P_A = 40\%$ $P_B = 50\%$	$P_A = 30\%$ $P_B = 40\%$	$P_A = 60\%$ $P_B = 50\%$
Number of S assumed (cf. table S_1)	589	323	589	483	323	483	642	589	642
Multiplication-factor cf Kaae I, II and III		3 1			4 6			9 9	
Numbers of patients required	1,800 ±	1,000 ±	1,800 ±	2,200 ±	1,500 ±	2,200 ±	6,400 ±	5,800 ±	6,400 ±

1) Results in percentages actually found

2) P_A and P_B indicate assumed population survival rates from McWhirter's method and Extended radical mastectomy respectively.

§ 3. *Paterson's Ovarian Radiation Trial*

Paterson's first trial (1959a, 1962), was designed to evaluate the contribution made by castration in a menopausal* group of women with cancer of the breast. The problem he set himself was to establish whether X-ray sterilization of the ovaries at the earliest possible moment in menopausal women could materially affect the course of the disease.

All breast cancer cases presenting at the Christie Hospital, Manchester, menopausal, and under 55 years of age were considered admissible to the trial, provided there were neither contra-indications to ovarian castration nor any special reason why it should be advised as a treatment of choice. The experimental sample for analysis consists of a varied selection of appropriate patients referred to the hospital for consideration for radiotherapy and allocated on a purely random basis either to have immediate ovarian irradiation (radiated group), or not to be so irradiated (control group). Either of these policies was quite independent of whatever other procedures were called

* For the purposes of Paterson's study menopausal women were defined as those before or at the menopause, or within 2 years thereafter.

for. A substantial proportion of the cases presenting postoperatively had, prior to operation presumptive stage I or stage II cancers of the breast (Manchester staging). These, as will be seen later, form the most important group in the study. The remainder included new but inoperable cases (stages III and IV, Manchester staging) and those recurrent either in the breast, axilla, or supraclavicular region, following an operation some time previously. The sample is not therefore a representative cross-section of all stages of breast cancer and in particular it should be appreciated that both early cases prior to operation and late cases for which hormone treatment was the only procedure possible are absent from the sample.

The study covered the period 1948-1955 and at completion the total sample consisted of 747 patients (10 year follow up: 744 patients) with breast cancer at various states of advancement but predominantly in a postoperative state when first seen and considered for ovarian radiation.

Paterson made a division of his series into the following subgroups:

a. Two major subgroups according to the status of the patient when first reviewed for possible ovarian radiation: –
   1. postoperative cases – patients admitted to the trial shortly after mastectomy and clinically free from demonstrable disease, and,
   2. inoperable or late cases – patients unsuitable for operation when first seen or with recurrent or residual disease.
b. Two age groups ($<$ 45 years and 45–54 years).
c. The postoperative group was divided into two subgroups according to whether malignant invasion was or was not found in the axillary nodes after operation, i.e. the contrast separately for proved surgical stage I and other cases.

Paterson used three criteria to state the results of the postoperative group. These criteria are Crude survival rate, Recurrence rate breast area (including axillary and supraclavicular nodes) and Manifestation of distant metastases.

The 10 year results of Paterson's ovarian radiation trial are recorded by Cole (1968). Cole's figures were used in our approach, except for table Paterson IV, where Paterson's 5 year figures are employed. In the tables referring to both trials of Paterson, the symbol X_m has a different notation than in the other trials considered in this chapter. Paterson worked with selected groups of patients and does not state the percentage of all available mammary carcinoma patients which these groups comprised. Therefore we can only calculate the number of patients of the selected group which according to our criteria is required for a trial as intended by Paterson. For the sake of uniformity, this number is indicated by X_m.

In the other tables, X_m stands for the number of unselected mammary carcinoma patients required, which is naturally larger.

TABLE PATERSON I. *Ovarian radiation and Control groups compared (10 years crude survival rate). No division into subgroups.*

I	Numbers of patients included in PATERSON'S clinical trial	744 100%	
II	Numbers of patients meeting requirements	Type of case not considered	
		Age not considered	
		Axillary involvement not considered	
	Therapies considered	Radiated	Control
III	Numbers of patients per therapy group	369	375
IV	Results in percentages (10 years crude survival rate)	46 6%	41.6%
V	Statistical significance (COLE)	p = 0 17	

Numbers of patients required according to our criteria

VI	Percentage of entire series meeting the requirements		100%
	Multiplicationfactor	$2 \times \frac{100}{F}$	$2 \times \frac{100}{100} = 2.0$

If a 10% difference in population survival rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 50\%$ $P_B = 40\%$
VIII	Number of S (cf. table S_1)		642
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	$2 \times 642 = 1{,}300 \pm$

If a 20% difference in population survival rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 60\%$ $P_B = 40\%$
VIII	Number of S (cf table S_1)		161
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	$2 \times 161 = 320 \pm$

P_A and P_B indicate the assumed population survival rates of Radiation and Control groups respectively.

TABLE PATERSON II. *Ovarian radiation and Control groups compared (10 years crude survival rate). Subdivision into Direct postoperative and Late Postoperative groups.*

I	Numbers of patients included in PATERSON'S clinical trial	744 100%			
II	Numbers of patients meeting requirements	Direct postoperative 596 80.2%		Late postoperative 148 19.8%	
		Age not considered			
		Axillary involvement not considered			
	Therapies considered	Radiated	Control	Radiated	Control
III	Numbers of patients per therapy group	293	303	76	72
IV	Results in percentages (10 years crude survival rate)	54.9%	47.5%	14.5%	16.7%
V	Statistical significance (COLE)	p = 0.07		p = 0.89 (not recorded by Cole)	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	80.2%		19.8%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{80.2} = 2.5$		$2 \times \frac{100}{19.8} = 10.1$	
	If a 10% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 50\%$ $P_B = 40\%$		$P_A = 10\%$ $P_B = 20\%$	
VIII	Number of S (cf. table S_1)	642		323	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$2.5 \times 642 = 1,600 \pm$		$10.1 \times 323 = 3,000 \pm$	
	If a 20% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 60\%$ $P_B = 40\%$		$P_A = 10\%$ $P_B = 30\%$	
VIII	Number of S (cf. table S_1)	161		98	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$2.5 \times 161 = 400 \pm$		$10.1 \times 98 = 1,000 \pm$	
	If a 30% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	— —		$P_A = 10\%$ $P_B = 40\%$	
VIII	Number of S (cf. table S_1)	—		50	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	—		$10.1 \times 50 = 500 \pm$	

P_A and P_B indicate the assumed population survival rates of Radiation and Control groups respectively.

TABLE PATERSON III. *Ovarian radiation and Control groups compared (10 years recurrence rate breast area and 10 years manifestation of distant metastases). Only Direct postoperative patients considered.*

I	Numbers of patients included in PATERSON'S clinical trial	744 100%			
II	Numbers of patients meeting requirements	Direct post-operative 596 80 2%			
		Age not considered			
		Axillary involvement not considered			
	Therapies considered	Radiated	Control	Radiated	Control
III	Numbers of patients per therapy group	293	303	293	303
IV	Results in percentages	10 years recurrence rate breast area (including axillary and supraclavicular nodes)		Manifestation of distant metastases (10 years follow up)	
		23 2%	29 7%	46 1%	54 5%
V	Statistical significance (COLL)	p = 0 07		p = 0 04	

Numbers of patients required according to our criteria

VI	Percentage of entire series meeting the requirements	80 2%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{80\,2} = 2\,5$	

If a 10% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 20% P_B = 30%	P_A = 40% P_B = 50%
VIII	Number of S (cf table S_1)	483	642
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	2 5 × 483 = 1,200 ±	2 5 × 642 = 1,600 ±

If a 20% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 20% P_B = 40%	P_A = 40% P_B = 60%
VIII	Number of S (cf table S_1)	133	161
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	2 5 × 133 = 350 ±	2,5 × 161 = 400 ±

P_A and P_B indicate the assumed population result percentages by Radiation and Control groups respectively.

TABLE PATERSON IV. *Ovarian radiation and Control groups compared (5 years mortality). Subdivision according to age.*

I	Numbers of patients included in PATERSON'S clinical trial	747 100%			
II	Numbers of patients meeting requirements	Type of case not considered			
		< 45 years 444 59 5%		45-54 years 303 40 5%	
		Axillary involvement not considered			
	Therapies considered	Radiated	Control	Radiated	Control
III	Numbers of patients per therapy group	226	218	143	160
IV	Results in percentages (5 years mortality)	46%	52%	35%	42%
V	Statistical significance (PAILRSON)	p = 0 3		p = 0 2	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	59 5%		40 5%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{59\,5} = 3\,4$		$2 \times \frac{100}{40\,5} = 4\,9$	
	If a 10% difference in population mortality rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 40\%$ $P_B = 50\%$		$P_A = 30\%$ $P_B = 40\%$	
VIII	Number of S (cf table S_1)	642		589	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$3\,4 \times 642 - 2{,}200 \pm$		$4\,9 \times 589 = 2{,}900 \pm$	
	If a 20% difference in population mortality rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 40\%$ $P_B = 60\%$		$P_A = 30\%$ $P_B = 50\%$	
VIII	Number of S (cf table S_1)	161		154	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$3\,4 \times 161 = 550 \pm$		$4\,9 \times 154 = 750 \pm$	

P_A and P_B indicate the assumed population mortality rates of Radiation and Control groups respectively

TABLE PATERSON V. *Ovarian radiation and Control groups compared (10 years crude survival rate). Only Direct postoperative patients considered. Subdivision according to axillary involvement.*

I	Numbers of patients included in PATERSON'S clinical trial	744 100%			
II	Numbers of patients meeting requirements	Direct postoperative			
		Age not considered			
		Axilla not involved 193 32.4%		Axilla involved 403 67.7%	
	Therapies considered	Radiated	Control	Radiated	Control
III	Numbers of patients per therapy group	90	103	203	200
IV	Results in percentages (10 years crude survival rate)	80%	68%	43.8%	37%
V	Statistical significance (COLE)	p = 0.06		p = 0.16	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	32.4		67.6	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{32.4} = 6.2$		$2 \times \frac{100}{67.6} = 3.0$	
	If a 10% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 80\%$ $P_B = 70\%$		$P_A = 40\%$ $P_B = 30\%$	
VIII	Number of S (cf. table S_1)	483		589	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$6.2 \times 483 = 3{,}000 \pm$		$3.0 \times 589 = 1{,}800 \pm$	
	If a 20% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 80\%$ $P_B = 60\%$		$P_A = 50\%$ $P_B = 30\%$	
VIII	Number of S (cf table S_1)	133		154	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$6.2 \times 133 = 800 \pm$		$3.0 \times 154 = 450 \pm$	

P_A and P_B indicate the assumed population survival rates of Radiation and Control groups respectively.

In studying the results of Paterson's ovariectomy trial, it appears that reliable general conclusions can be drawn from the direct postoperative series (cf. Paterson's tables I and III). The reader will have noted that for this group, Paterson finds significant or nearly significant figures from his total of 744 patients, whereas the numbers calculated by us are higher (cf table V-1).

TABLE V-1.

Criterion	Difference in results	Statistical significance	X_m as calculated by us
Crude survival rate cf. table Paterson II	7.4%	p = 0.07	1600
Recurrence rate breast area cf. table Paterson III	6.5%	p = 0.07	950
Manifestation of distant metastases cf. table Paterson III	8.4%	p = 0.04	1300

Suppose the 5 year survival chances are $P_A = 40\%$, $P_B = 60\%$. In this case, according to table Paterson I, we require 161 patients per treatment group to demonstrate this difference with 95% probability. This means: in 95% of the cases in which, with $P_A = 40\%$, $P_B = 60\%$ we carry out a trial with 161 patients per treatment group, weshall find two percentages of survival, $\hat{P}_A$ and $\hat{P}_B$ which differ significantly according to the χ^2-test for a 2×2 table. In 5% of the cases the values found for $\hat{P}_A$ and $\hat{P}_B$ will not differ significantly. This is due to the fact that $\hat{P}_A$ and $\hat{P}_B$ depend on chance; they may assume different values in the vicinity of survival probabilities P_A and P_B; sometimes these values will not differ sufficiently to justify the conclusion that $P_A < P_B$.

Now suppose we take only 100 patients per treatment group, which according to our criterion is 'insufficient'. Nevertheless (according to table A1 in the Appendix), there is still more than an 81% probability that a significant result will be obtained, in other words, this is still quite possible. Calculation according to our criteria shows that with the patient material available, differences can be demonstrated between the irradiated and the control group of 20% or more. This also applies when we classify according to age and to pathology of the axillary glands. It is regrettable that Paterson did not study a subdivision on the basis of a combination of these characteristics. When two characteristics, either singly or in combination, exert a slight favorable effect on the prognosis, it is possible that this favorable influence will only manifest itself with significant figures when these characteristics are studied in combination. However, owing to the size of this series of Paterson, further subdivision leads to too small subgroups. If we suppose that in Paterson's patient material the occurrence of axillary involvement and the age are independent selection criteria, we can calculate the size of the smallest subgroup formed by patients with the characteristics 'axilla not involved' and 'age 45–54 years'. The frequencies of these characteristics are 40.5% and 32.4% respectively (cf. Paterson IV and V). Accordingly we may estimate that a combination of these characteristics will occur in $\frac{40.5}{100} \cdot \frac{32.4}{100} = 13.1\%$ of cases, or about 100 patients. With a subdivision into treatment groups of equal size, this would still make it possible to demonstrate a difference of 30 to 40% between the chances of results (cf. table S1).

In Ch. III §3 p. 14, a possible difference in survival curves between two groups is considered.

Cole (1968) describes such a phenomenon:

'By the end of the 1st year 12.6 per cent of the irradiated group had developed signs of recurrence or metastases, while 24.4 per cent of the control group had evidence of disease. This difference is highly significant ($p = 0.0002$).

Year by year the incidence of recurrence or metastases in the irradiated group is less than in the control group. It is interesting to note that by the end of 10 years 47.4 per cent of the irradiated group showed evidence of active disease or had died while the comparable figure of 48.2 per cent was reached in the control group 6 years earlier, *i.e.* at the end of the 4th year.

The cumulative incidence of recurrent disease in the group who had negative axillary nodes is given in table V-2. In the first year there is little difference between the irradiated and the control groups (4.4 per cent compared with 6.8 per cent) but this is to be expected as all these patients had early disease when included in the trial. However, year by year through the table there is a postponement of the development of active disease in the irradiated group. By the end of the 7th year 21.1 per cent of the treated group had active disease, a figure similar to that already reached at the end of 3 years for the control group (21.4%).

TABLE V-2. *Relative incidence of recurrence of malignancy to 10th anniversary or to death within that period for group with negative axillary nodes.*

	Number of cases		Cumulative incidence %	
Years after treatment	Irradiated	Control	Irradiated	Control
Within 1 yr.	90	103	4.4	6.8
„ 2 „			8.9	14.6
„ 3 „			14.4	21.4
„ 4 „			17.8	25.2
„ 5 „			16.7	27.2
„ 7 „			21.1	33.0
„ 10 „			24.4	35.9

The results for the patients with positive axillary nodes are presented in table V-3, from which it is seen that at 1 year there is a highly significant difference between the recurrence rates in the irradiated and control groups ($p = 0.00006$). The same delay in the onset of active disease is seen year by year as in the previous tables. At 10 years 57.6 per cent of the irradiated group had active disease, a figure comparable to that of 57 per cent for the control group, reached at the end of 3 years.

TABLE V-3. *Relative incidence of recurrence of malignancy to 10th anniversary or to death within that period for group with positive axillary nodes.*

	Number of cases		Cumulative incidence %	
Years after treatment	Irradiated	Control	Irradiated	Control
Within 1 yr.	203	200	16.3	33.5
„ 2 „			33.0	51.0
„ 3 „			41.9	57.0
„ 4 „			44.8	60.0
„ 5 „			50.7	61.5
„ 7 „			53.7	63.0
„ 10 „			57.6	67.0

From these results it would appear that ovarian irradiation prolongs the time between the treatment of primary disease and the later development of recurrence'.

§ 4. *Paterson's Postoperative Radiotherapy Trial*

Paterson's second trial attempted to evaluate routine postoperative radiotherapy (1959b).

The criteria for acceptance of patients into the trial were:

1. Female patients with histologically verified mammary carcinoma.
2. Under 70 years of age.
3. All patients without exception had undergone a standard radical mastectomy of the Halsted type for stage I or stage II mammary carcinoma, with possibly a small minority of early stage III cases (Manchester staging).
4. Having had no other treatment.
5. Being clinically free of demonstrable residue or distant metastases.
6. Having no evidence in the surgical description of the operation to suggest that the operation was thought to have been incomplete.
7. Having no reason for the adoption of a 'watch' policy as a treatment of choice, for example on account of concomitant disease.

Paterson compared prophylactic irradiation in one group shortly after operation with a careful watch policy in another group, with irradiation only on the first actual evidence of relapse. Two different but both radical X-ray techniques were used. One primarily involved irradiation of the breast flap and axilla (quadrate technique), and the other primarily involved irradiation of the axillary, supraclavicular and parasternal lymph node drainage areas (peripheral technique). The study covered the period 1949–1955 and included 709 patients treated and 752 watched. Paterson made a subdivision of the series according to age and axillary involvement. As a measure of results of therapy the 7 years crude survival rate was used.

In a 10 year analysis, Easson (1968) makes a division into stage I and stage II cases in evaluating recurrence rates. Although Paterson, as in his ovariectomy trial, used a selected group of patients, we for the sake of uniformity use the symbol X_m (cf. Ch. V, p. 69).

TABLE PATERSON VI. *Treated and Watched groups compared (7 years mortality rate and 10 years local recurrence rate). Technique not considered. No division into subgroups.*

I	Numbers of patients included in PATERSON'S clinical trial	1,461 100 %			
	Postoperative radiotherapy	Technique not considered			
II	Numbers of patients meeting requirements (Data on clinical classification not recorded by PATERSON)	Age not considered			
		Axillary involvement not considered			
	Therapies considered	Treated	Watched	Treated	Watched
III	Numbers of patients per therapy group	709	752	709	752
IV	Results in percentages	7 years mortality rate 53%	51%	10 years local recurrence rate 19%	32%
V	Statistical significance (not recorded by PATERSON and EASSON) X^2 test : p value	$p = 0.47$		$p < 10^{-5}$	

Numbers of patients required according to our criteria

VI	Percentage of entire series meeting the requirements	100%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{100} = 2.0$	

If a 10% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 60\%$ $P_B = 50\%$	$P_A = 20\%$ $P_B = 30\%$
VIII	Number of S (cf. table S_1)	642	483
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$2.0 \times 642 = 1{,}300 \pm$	$2.0 \times 483 = 950 \pm$

P_A and P_B indicate the assumed population mortality or local recurrence rates of Treated and Watched groups respectively.

TABLE PATERSON VII. *Treated and Watched groups compared (10 years local recurrence rate). Technique not considered. Subdivision into Stage I and Stage II cases.*

I	Numbers of patients included in PATERSON'S clinical trial	1,461 100%			
	Postoperative radiotherapy	Technique not considered			
II	Numbers of patients meeting requirements	Stage I 527 36 1%		Stage II 934 63 9%	
		Age not considered			
		Axillary involvement not considered			
	Therapies considered	Treated	Watched	Treated	Watched
III	Numbers of patients per therapy group	not recorded		not recorded	
IV	Results in percentages (10 years local recurrence rate)	9 5%	16 0%	25 0%	41 5%
V	Statistical significance (not recorded by EASSON) X^2 test p value	$p = 0\,035$		$p < 10^{-5}$	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	36 1%		63 9%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{36\,1} = 5\,5$		$2 \times \frac{100}{63\,9} = 3\,1$	
	If a 10% difference in population local recurrence rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 10\%$ $P_B = 20\%$		$P_A = 20\%$ $P_B = 30\%$	
VIII	Number of S (cf table S_1)	323		483	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$5\,5 \times 323 = 1,750 \pm$		$3.1 \times 483 = 1,500 \pm$	
	If a 20% difference in population local recurrence rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 10\%$ $P_B = 30\%$		$P_A = 20\%$ $P_B = 40\%$	
VIII	Number of S (cf table S_1)	98		133	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$5\,5 \times 98 = 550 \pm$		$3\,1 \times 133 = 400 \pm$	

P_A and P_B indicate the assumed population local recurrence rates for Treated and Watched groups respectively.

TABLE PATERSON VIII. *Treated and Watched groups compared (7 years crude survival rate). Technique not considered. Subdivision according to age.*

I	Numbers of patients included in PATERSON'S clinical trial	1,461 100%			
	Postoperative radiotherapy	Technique not considered			
II	Numbers of patients meeting requirements (Data on clinical classification are not recorded by PATERSON)	< 50 years 623 42 7%		> 50 years 838 57 3%	
		Axillary involvement not considered			
	Therapies considered	Treated	Watched	Treated	Watched
III	Numbers of patients per therapy group	Not recorded	Not recorded	Not recorded	Not recorded
IV	Results in percentages (7 years crude survival rate)	54 0%	45 0%	53 0%	55 0%
V	Statistical significance (not recorded by PATERSON) X^2 test p value (therapy groups assumed to be equal)	p = 0 03		p = 0 64	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	42 7%		57 3%	
	Multiplication factor $2 \times \frac{100}{F}$	$2 \times \frac{100}{42\ 7} = 4\ 7$		$2 \times \frac{100}{57\ 3} = 3\ 5$	
	If a 10% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 50% P_B = 40%		P_A = 50% P_B 60%	
VIII	Number of S (cf table S_1)	642		642	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	4 7 × 642 = 3,000 ±		3 5 × 642 = 2,200 ±	
	If a 20% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed round result percentages) for entering table S_1	P_A = 60% P_B = 40%		P_A = 50% P_B = 70%	
VIII	Number of S cf table S_1)	161		154	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	4 7 × 161 = 750 ±		3 5 × 154 = 550 ±	

P_A and P_B indicate the assumed population survival rates of Treated and Watched groups respectively

TABLE PATERSON IX. *Radiation (Quadrate technique) and Control groups compared (7 years crude survival rate) Subdivision according to axillary involvement.*

I	Numbers of patients included in PATERSON'S clinical trial	1,461 100%			
	Postoperative radiotherapy A Quadrate technique B Peripheral technique	Quadrate technique 720 49 3%			
II	Numbers of patients meeting requirements (Data on clinical classification are not recorded by PATERSON)	Age not considered			
		Axilla not involved 247 16 8%		Axilla involved 473 32 4%	
	Therapies considered	Treated	Watched	Treated	Watched
III	Numbers of patients per therapy group	105	142	222	251
IV	Results in percentages (7 years crude survival rate)	36 2%	27 3%	63 5%	65 5%
V	Statistical significance (not recorded by PATERSON) χ^2 test p value	p = 0 19		p = 0 73	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	16 8%		32 4%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{16\,8} - 11\,9$		$2 \times \frac{100}{32\,4} = 6\,2$	
	If a 10% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A 30% P_B = 20%		P_A = 70% P_B = 60%	
VIII	Number of S (cf table S_1)	483		589	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	11 9 × 483 = 5,700 ±		6 2 × 589 = 3,600 ±	
	If a 20% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 40% P_B = 20%		P_A = 70% P_B = 50%	
VIII	Number of S (cf table S_1)	133		154	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	11 9 × 133 = 1,600 ±		6 2 × 154 = 950 ±	

P_A and P_B indicate the assumed population survival rates of Treated and Watched groups respectively

TABLE PATERSON X. *Radiated (Peripheral technique) and Control groups compared (7 years crude survival rate). Subdivision according to axillary involvement.*

I	Numbers of patients included in PATERSON'S clinical trial	1,461 100%			
	Postoperative radiotherapy A. Quadrate technique B Peripheral technique	Peripheral technique 741 50 7%			
II	Numbers of patients meeting requirements (Data on clinical classification are not recorded by PATERSON)	Age not considered			
		Axilla not involved 281 19 2%		Axilla involved 460 31 5%	
	Therapies considered	Treated	Watched	Treated	Watched
III	Numbers of patients per therapy group	139	142	243	217
IV	Results in percentages (7 years crude survival rate)	37 0%	36 0%	58 0%	56 0%
V	Statistical significance (not recorded by PATERSON) χ^2 test p value	p = 1 0		p = 0 69	
	Numbers of patients required according to our criteria				
VI	Percentage of entire series meeting the requirements	19 2%		31 5%	
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{19\,2} = 10\,4$		$2 \times \frac{100}{31\,5} = 6\,3$	
	If a 10% difference in population survival rate has to be detected				
VII	Values of P_A anf P_B assumed (round result percentages) for entering table S_1	P_A = 40% P_B = 30%		P_A = 60% P_B = 50%	
VIII	Number of S (cf table S_1)	589		642	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$10\,4 \times 589 = 6{,}000 \pm$		$6\,3 \times 642 = 4{,}000 \pm$	
	If a 20% difference in population survival rate has to be detected				
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	P_A = 50% P_B = 30%		P_A = 60% P_B = 40%	
VIII	Number of S (cf table S_1)	154		161	
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$10\,4 \times 154 = 1{,}600 \pm$		$6\,3 \times 161 = 1{,}000 \pm$	

P_A and P_B indicate the assumed population survival rates of Treated and Watched groups respectively.

According to our criteria, the number of patients in Paterson's postoperative irradiation trial would be sufficient to demonstrate a possible difference of 10% between the population result rates P_A and P_B with a probability of 95% (cf. table Paterson VI) if no subdivisions were made according to selection criteria (age, stage of pathology of the axillary glands).

If a subdivision is made on the basis of one of these criteria, it will in general only be possible to demonstrate differences of the order of 20% between P_A and P_B with a probability of 95%. As noted in connection with Paterson's ovariectomy trial, one might consider organizing a trial with subgroups corresponding to a combination of two or more of the selection criteria. For instance, if Paterson had combined the criteria age $<$ 50 years (42.7% cf. table Paterson VIII) and 'axilla not involved' (19.2% cf. table Paterson X) into one subgroup, and these selection criteria had been regarded as independent of one another. it may be estimated that only $\frac{42.7}{100} \times \frac{19.2}{100} = 8.2\%$ of the patient material would have fulfilled the conditions. This amounts to about 100 patients. With a subdivision into treatment groups of equal size, this would still have permitted demonstration of a difference of 30 to 40% between the population result rates. Paterson's trial (cf. table Paterson VI) clearly shows how, when two methods of treatment are compared, no difference may be found for one criterion, while there *is* a difference for a different criterion. While the 7 year mortality rates of the treated and watched groups amount to 53% and 51% respectively (the 10 year mortality rate in the two groups together is 55%), we find there is a significant difference in the 10 year local recurrence rates (19.0% and 32.0% respectively).

We can also see from Paterson's table VI that the numbers of patients required for the various success criteria differ, because the value of S is influenced by the percentage of results ('7 years mortality rate': 1300 $\pm$ patients. '10 years local recurrence rate': 950 $\pm$ patients). In this trial, significant differences continue to occur even after subdivision into stages I and II. According to our criteria, there were almost enough patients to demonstrate a difference of 10% in result with a probability of 95%, and ample to demonstrate a difference of 20%. If in this trial the factor 'curative operability' is taken into account, a slight decrease in X_m results.

If in this trial the factor 'curative operability' is taken into account a considerable decrease in X_m is possible.

Paterson's data showed that the 3 year mortality was about 30%. If in the final analysis this group would be excluded from the trial, only 70 out of every 100 patients remain for investigation. We considered the case $P_A = 60\%$ and $P_B = 50\%$, 7 year population mortality rate; therefore the value of S is S = 642 and X_m is 2×642, or about 1300.

If the 3 year mortality is the same in both therapygroups, the mortality between 3 and 7 years was 30% and 20% respectively, with respect to number of operable patients $\frac{0.3}{0.7} - 42.9\%$ and $\frac{0.2}{0.7} = 28.6\%$. The number S for the operable patients according to formula (2) of the Appendix now is equal to 290. And thus $X_m = 2 \times \frac{100}{70} \times 290 = 830 \pm$.

This is a reduction of about 65% with respect to the number $X_m = 1300$ required if the inoperable patients are not excluded.

§ 5. *Nissen-Meyer's Ovariectomy Trial*

Nissen-Meyer (1965; 1968) describes his trial as follows:

'Between 22nd November 1957 and 31st December 1963, 932 women under the age of 70 years were admitted as in-patients for the initial treatment of histologically proved operable cancer of the breast. Following histological examination of the axillary nodes, 455 patients were classified as stage 1 and 447 as stage 2. The histology of the axillary nodes was not known in thirty patients, who were classified as stage 1 or 2.

All patients were included in a prospective study of 'prophylactic' versus 'therapeutic' castration. Six hundred and sixty-four had suppression of ovarian function (74 by surgical oophorectomy, 590 by ovarian irradiation) as part of the primary treatment. The remaining 268 cases did not have immediate castration, but it was planned that this should be performed as soon as recurrence was diagnosed. All other forms of therapy were kept as standardized as possible. Inclusion in a controlled clinical trial with random allocation was considered ethically justified in 448 of these patients. Full details of the methods of allocation to different groups, treatment, and analysis of results have been given previously (Nissen-Meyer, 1965).

In this paper an attempt has been made to ascertain whether castration performed as an adjuvant to radical mastectomy, (1) increases the symptom-free interval in those patients destined to develop recurrence, (2) prolongs survival to a greater extent than if postponed until recurrence occurs, (3) is beneficial to postmenopausal patients, and (4) gives equal results when performed surgically or by radiation.'

TABLE NISSEN-MEYER I. *(according to original subdivision of series, but not used by* NISSEN-MEYER *in his trial).*

Ovariectomy and Control groups compared (3 yr. and 5 yr. crude survival rates). Only premenopausal patients considered.

Subdivision into subgroups according to age, clinical stage, malignancy grade and localization of tumor.

I	Numbers of patients available in NISSEN-MEYER'S study		1,442 100%									
II	Numbers of patients meeting requirements	Included only stages I and II under 70	902 62 4%									
		Premenopausal	418 29 2%									
		Clinical stage	I 217 15 3%				II 201 13 9%					
		Malignancy grade (histologically)	I+II 141 9 7%				III+IV 76 5 3%		I+II 45 3 1%		III+IV 15 10 8%	
		Localization	Lateral 80 5 6%		Medial 61 4 2%		–		–		–	
	Therapies considered		Castration	Control	Castration	Control	Castration	Control	Castration	Control	Castration	Control
III	Numbers of patients per therapy group		42	38	29	32	41	35	39	6	154	2
	Years' follow up		5		3		5		5		5	
IV	Results in percentages (crude survival rate)		92 3 %	94.6 %	82 8 %	96 5 %	86.0 %	100 0 %	85 4 %	–	68 1 %	–
V	Statistical significance (not recorded by NISSEN-MEYER) χ^2 test : p value		p = 1 0		p = 0 11		p = 0 03		–		–	

	Numbers of patients required according to our criteria					
VI	Percentage of entire series meeting the requirements	56%	42%	53%	–	–
	Multiplicationfactor $2 \times \frac{100}{F}$	$2 \times \frac{100}{56} = 35.7$	$2 \times \frac{100}{42} = 47.6$	$2 \times \frac{100}{53} = 37.7$	–	–
	If a 10% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 90\%$ $P_B = 100\%$	$P_A = 80\%$ $P_B = 90\%$	$P_A = 90\%$ $P_B = 100\%$	–	– –
VIII	Number of S (cf table S_1)	63	323	63	–	–
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$35.7 \times 63 = 2{,}250 \pm$	$47.6 \times 323 = 15{,}500 \pm$	$37.7 \times 63 = 2{,}350 \pm$	–	–
	If a 20% difference in population survival rate has to be detected					
VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 80\%$ $P_B = 100\%$	$P_A = 80\%$ $P_B = 100\%$	$P_A = 80\%$ $P_B = 100\%$		
VIII	Number of S (cf table S_1)	31	31	31	–	–
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$35.7 \times 31 = 1{,}100 \pm$	$47.6 \times 31 = 1{,}500 \pm$	$37.7 \times 31 = 1{,}150 \pm$	–	–
	If a 30% difference in population survival rate has to be detected					
VIII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	– –	$P_A = 70\%$ $P_B = 100\%$	– –	– –	– –
VIII	Number of S (cf table S_1)	–	20	–	–	–
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	–	$47.6 \times 20 = 950 \pm$	–	–	–

P_A and P_B indicate the assumed population survival rates of Castration and Control groups respectively

TABLE NISSEN-MEYER II *(according to original subdivision of series, but not used by* NISSEN-MEYER *in his trial).*

Ovariectomy and Control groups compared (3 yr. and 5 yr. crude survival rate). Only postmenopausal patients considered.

Subdivision into subgroups according to age, clinical stage, malignancy grade and localization of tumor.

I	Numbers of patients available for NISSEN-MEYER'S study		1,442 100%									
II	Numbers of patients meeting requirements	Included only stages I and II under 70	902 62.4%									
		Postmenopausal	484 33.6%									
		Clinical stage	I 238 16.5%						II 246 17.1%			
		Malignancy grade (histologically)	I+II 141 9.8%				III + IV 97 6 7%		I+II 49 3 4%		III+IV 197 13.7%	
		Localization	Lateral 74 5.1%		Medial 67 4.6%		–		–		–	
	Therapies considered		Castration	Control	Castration	Control	Castration	Control	Castration	Control	Castration	Control
III	Numbers of patients per therapy group		53	21	47	20	68	29	34	15	140	57
	Years' follow up		4		4		5		2		6	
IV	Results in percentages (crude survival rate)		92.4 %	77.0 %	94 0 %	79.1 %	87 4 %	80 6 %	79.7 %	71.8 %	51.4 %	40 8 %
V	Statistical significance (not recorded by NISSEN-MEYER) χ^2 test : p value		p = 0.13		p = 0.21		p = 0.10		p = 0.72		p = 0.21	

Numbers of patients required according to our criteria

VI	Percentage of entire series meeting the requirements	51%	46%	67%	34%	137%
	Multiplication factor $2 \times \frac{100}{F}$	$2 \times \frac{100}{51} = 39.2$	$2 \times \frac{100}{46} = 43.5$	$2 \times \frac{100}{6.7} = 29.9$	$2 \times \frac{100}{34} = 58.8$	$2 \times \frac{100}{137} = 14.6$

If a 10% difference in population survival rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 90\%$ $P_B = 80\%$	$P_A = 90\%$ $P_B = 80\%$	$P_A = 90\%$ $P_B = 80\%$	$P_A = 80\%$ $P_B = 70\%$	$P_A = 50\%$ $P_B = 40\%$
VIII	Number of S (cf table S_1)	323	323	323	483	642
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$39.2 \times 323 = 12{,}500 \pm$	$43.5 \times 323 = 14{,}000 \pm$	$29.9 \times 323 = 9{,}500 \pm$	$58.8 \times 483 = 28{,}500 \pm$	$14.6 \times 642 = 9{,}500 \pm$

If a 20% difference in population survival rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 90\%$ $P_B = 70\%$	$P_A = 90\%$ $P_B = 70\%$	$P_A = 90\%$ $P_B = 70\%$	$P_A = 80\%$ $P_B = 60\%$	$P_A = 60\%$ $P_B = 40\%$
VIII	Number of S (cf table S_1)	98	98	98	133	161
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$39.2 \times 98 = 3{,}800 \pm$	$43.5 \times 98 = 4{,}300 \pm$	$29.9 \times 98 = 2{,}900 \pm$	$58.8 \times 133 = 7{,}800 \pm$	$14.6 \times 161 = 2{,}350 \pm$

If a 30% difference in population survival rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 90\%$ $P_B = 60\%$	$P_A = 90\%$ $P_B = 60\%$	$P_A = 90\%$ $P_B = 60\%$	$P_A = 90\%$ $P_B = 60\%$	$P_A = 60\%$ $P_B = 30\%$
VIII	Number of S (cf table S_1)	50	50	50	50	70
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$39.2 \times 50 = 1{,}950 \pm$	$43.5 \times 50 = 2{,}200 \pm$	$29.9 \times 50 = 1{,}500 \pm$	$58.8 \times 50 = 3{,}000 \pm$	$14.6 \times 70 = 1{,}000 \pm$

If a 40% difference in population survival rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1	$P_A = 90\%$ $P_B = 50\%$	$P_A = 90\%$ $P_B = 50\%$	– –	$P_A = 90\%$ $P_B = 50\%$	–
VIII	Number of S (cf table S_1)	31	31	–	31	–
IX	Numbers of patients required on the basis of our criteria $X_m = S \times 2 \times \frac{100}{F}$	$39.3 \times 31 = 1{,}200 \pm$	$43.5 \times 31 = 1{,}300 \pm$	–	$58.8 \times 31 = 1{,}750 \pm$	–

P_A and P_B indicate the assumed population survival rates of Castration and Control groups respectively.

TABLE NISSEN MEYER III. *Ovariectomy and Control groups compared in premenopausal patients (8 years % free from disease and % crude survival) in stage I cases. Surgical and Radiological ovariectomy groups compared (7 years % free of disease and 8 years % crude survival) in stage II cases. No further division into subgroups.*

I	Numbers of patients available for NISSEN-MEYER'S study	1,442 100%							
II	Numbers of patients meeting requirements Including only stages I and II under 70	902 62.4%							
	Premenopausal	418 29 2%							
	Included in clinical trial according to prognostic signs and ethically acceptable	Stage I 161 11.2%				Stage II 112 7 8%			
	Therapies considered	Castration and Control				Surgical and Radiological castration			
III	Numbers of patients per therapy group	Allocated at random				Allocated at random			
	Years' follow up	8		8		7		8	
	Results in percentages (taken from NISSEN-MEYER'S graphs)	% free from disease		% crude survival		% free from disease		% crude survival	
IV		Castration	Control	Castration	Control	Surgical castration	Radiological castration	Surgical castration	Radiological castration
		80% ±	90% ±	80% ±	90% ±	50% ±	60% ±	50% ±	50% ±
V	Statistical significance (not recorded by NISSEN-MEYER) χ^2 test p value	p = 0.12		p = 0.12		p = 0.34		p = 1	

Numbers of patients required according to our criteria

VI	Percentage of entire series meeting the requirements		11 2%		7 8%
	Multiplicationfactor	$2 \times \frac{100}{F}$	$2 \times \frac{100}{11\,2} = 17\,9$		$2 \times \frac{100}{7\,8} = 25\,6$

If a 10% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 80\%$ $P_B = 90\%$	$P_A = 80\%$ $P_B = 90\%$	$P_A = 50\%$ $P_B = 60\%$	$P_A = 50\%$ $P_B = 60\%$
VIII	Number of S (cf table S_1)		323	323	642	642
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	17 9 × 323 = = 5,800 ±	17 9 × 323 = = 5,800 ±	25 6 × 642 = = 16,500 ±	25 6 × 642 = = 16,500 ±

If a 20% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 70\%$ $P_B = 90\%$	$P_A = 70\%$ $P_B = 90\%$	$P_A = 40\%$ $P_B = 60\%$	$P_A = 40\%$ $P_B = 60\%$
VIII	Number of S (cf table S_1)		98	98	161	161
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	17 9 × 98 = = 1,750 ±	17 9 × 98 = = 1,750 ±	25 6 × 161 = = 4,000 ±	25 6 × 161 = = 4,000 ±

If a 30% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 60\%$ $P_B = 90\%$	$P_A = 60\%$ $P_B = 90\%$	$P_A = 40\%$ $P_B = 70\%$	$P_A = 40\%$ $P_B = 70\%$
VIII	Number of S (cf table S_1)		50	50	70	70
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	17 9 × 50 = = 900 ±	17 9 × 50 = = 900 ±	25 6 × 70 = = 1,800 ±	25 6 × 70 = = 1,800 ±

In stage I cases, P_A and P_B indicate assumed population "% free from disease" and "% crude survival" Primary castration and Control groups respectively, and in stage II cases Surgical castration and Radiological castration groups respectively.

TABLE NISSEN-MEYER IV. *Ovariectomy and Control groups compared in postmenopausal patients. (7 or 8 years % free from disease and 8 years % crude survival rates). Subdivision into stage I and stage II cases.*

I	Numbers of patients available for NISSEN-MEYER'S study	1,442 100%						
II	Numbers of patients meeting requirements Including only stages I and II under 70	902 62 4%						
	Postmenopausal	484 33 6%						
	Clinical stage	I 238 16 5%				II 246 17 1%		
	Included in clinical trial	80 5 6%				95 6 6%		
	Therapies considered	Castration and Control				Castration and Control		
III	Numbers of patients per therapy group	Allocated at random				Allocated at random		
	Years' follow up	8		8		7		8
	Results in percentages (from NISSEN-MEYER'S graphs)	% free from disease		% crude survival		% free from disease		% crude survival
IV		Castration	Control	Castration	Control	Castration	Control	Castration	Control
		75% ±	65% ±	70% ±	75% ±	40% ±	20% ±	40% ±	30% ±
V	Statistical significance (not recorded by NISSEN-MEYER)* χ^2 test p value	p = 0 46		p = 0 80		p = 0 06		p = 0 35	

*Nissen-Meyer notes that the differences had reached statistical significance 4 years after commencement of study.

Numbers of patients required according to our criteria

VI	Percentage of entire series meeting the requirements		56%	66%	
	Multiplicationfactor	$2 \times \frac{100}{F}$	$2 \times \frac{100}{56} = 35.7$	$2 \times \frac{100}{66} = 30.3$	

If a 10% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 80\%$ $P_B = 70\%$	$P_A = 70\%$ $P_B = 80\%$	$P_A = 30\%$ $P_B = 20\%$	$P_A = 40\%$ $P_B = 30\%$
VIII	Number of S (cf table S_1)		483	483	483	483
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	35.7 × 483 = = 17,000 ±	35.7 × 483 = = 17,000 ±	30.3 × 483 = = 14,500 ±	30.3 × 483 = = 14,500 ±

If a 20% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 80\%$ $P_B = 60\%$	$P_A = 60\%$ $P_B = 80\%$	$P_A = 40\%$ $P_B = 20\%$	$P_A = 40\%$ $P_B = 20\%$
VIII	Number of S (cf table S_1)		133	133	133	133
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	35.7 × 133 = = 4,800 ±	35.7 × 133 = = 4,800 ±	30.3 × 133 = = 4,000 ±	30.3 × 133 = = 4,000 ±

If a 30% difference in population result rate has to be detected

VII	Values of P_A and P_B assumed (round result percentages) for entering table S_1		$P_A = 90\%$ $P_B = 60\%$	$P_A = 60\%$ $P_B = 90\%$	$P_A = 40\%$ $P_B = 10\%$	$P_A = 40\%$ $P_B = 10\%$
VIII	Number of S (cf table S_1)		50	50	50	50
IX	Numbers of patients required on the basis of our criteria	$X_m = S \times 2 \times \frac{100}{F}$	35.7 × 50 = = 1,800 ±	35.7 × 50 = = 1,800 ±	30.3 × 50 = = 1,500 ±	30.3 × 50 = = 1,500 ±

P_A and P_B indicate the assumed population "% free from disease" and "% crude survival" of Primary castration and Control groups respectively

Nissen-Meyer's material consisted of 1,442 women admitted for primary treatment of histologically verified carcinoma of the breast between 1957 and 1963.

The design of Nissen-Meyer's clinical trial is a good example of the consequences of variegated division into subgroups according to prognostic factors (cf. tables Nissen-Meyer I and II).

In our tables we followed the subdivision suggested by Nissen-Meyer and computed the numbers of patients required on the basis of our criteria.

Since according to the author 902 patients could be regarded as suitable for inclusion in the trial on clinical grounds, and since he gives the division into subgroups of these 902 patients, we started our approximation with this number and calculated the percentage difference between castration and control groups that might be demonstrated by the Nissen-Meyer patient material (cf. tables Nissen-Meyer I and II) if all subgroups were considered separately. These examples have been worked out primarily to demonstrate the effects of subdivision carried to great lengths on the total number of patients required.

However, since Nissen-Meyer applied radical pre-selection on ethical grounds, the number of patients actually included in the trial was much smaller, and the subdivision based on prognostic factors was not carried out completely. This raises the question of the extent to which this intensive pre-selection affected the composition of the material, and even whether one is justified in calling this experiment a clinical trial at all (cf. Moeys' trial, Ch. II § 2).

In the premenopausal group, only 161 patients in stage I were randomly divided into a primary castration group and a control group. 112 premenopausal stage II patients were all subjected to primary castration and were divided at random into two groups in order to compare surgical and radiological ovariectomy (cf. table Nissen-Meyer III). In the postmenopausal group, 80 patients in stage I and 95 stage II cases were divided at random into a primary castration group and a control group (cf. table Nissen-Meyer IV).

As can be concluded from Nissen-Meyer's tables, his division into subgroups, however interesting in itself, produces so much fragmentation of the material that the numbers of patients per subgroup only would permit investigation on the basis of a difference of 40% in result rate between the two therapy groups.

If in this design of Nissen-Meyer's, every subgroup would have to be checked separately for the difference between radiological and surgical ovariectomy, every castration group would have to be subdivided again into two equal therapy groups, and X_m would have to be multiplied by a factor of 2. It is doubtful whether such an extensive trial would be worth while for mammary carcinoma, a condition in which no great differences in result are to be expected. It is possible, however, that a selection carried to greater lengths might in itself yield certain data, for instance if it appeared that in one particular subgroup the treatment administered gave a particularly good result. However, the planning of such a trial would give rise to considerable organizatory problems in view of the large number of patients required. Cooperation between numerous centers would then be necessary.

As regards the trial actually conducted by Nissen-Meyer (cf. tables Nissen-Meyer III and IV), we see that the series was nearly large enough to demonstrate a difference of 20% in population result rates in the pre-menopausal group. The post-menopausal group contained a sufficient number of patients to demonstrate a difference of 30% in population result rates. A publication by Nissen-Meyer (1968) shows that he found a significant difference between the two therapies after a follow up of 4 years. He also found significant differences in the 2nd and 3rd years of follow up of postmenopausal patients in stage III cases for the criterion '% free of disease'. For the criterion '% crude survival' he found significant differences in stage I cases in the 2nd year and in stage II cases in the 1st year. If only one significant difference is found for a single criterion, not too much significance should be attached to such an isolated event.

It is of course true that an occasional significant difference may still be encountered when the methods of treatment are actually equivalent (this probability is less than the level of significance, in our case 5%).

Matters are different when, as Nissen-Meyer reports in postmenopausal patients over 60 years of age for criterion '% free of disease', differences of the order of 20% are encountered in the 1st, 2nd, 3rd and 6th years of follow up.

Chapter I discusses the importance of controlled clinical trials in establishing the treatment that produces the best results in mammary carcinoma.

From the data at present available concerning the course and treatment of mammary carcinoma, it is not possible to indicate with any certainty what treatment would be best for a given patient with a given mammary carcinoma.

In our opinion the results so far obtained in retrospective studies of the results of various treatments include too many uncertainties to provide valid clinical guidelines, and our own series of 1500 patients with malignant disease of the breast illustrates this.

Our findings make clear that the mere preparation of a large and well documented series of patients is no guarantee that valid conclusions can be drawn from it. Neither will the inclusion of new groups of patients in the series solve the problem, for each subsequent group of patients has its own uncertainties, so that including new groups of patients in the material only adds new uncertainties. Investigations to solve this problem are an urgent necessity, and controlled clinical trials seem to be the only method for such investigations.

A controlled clinical trial is an investigation in which two or more methods of treatment for a well defined disease are compared on similarly composed groups of patients. The trial should aim at answering a definite question, and meet the requirements of sound statistical analysis. The design of such trials will have to be similar to that of a laboratory experiment.

Both during discussions in the Committee on the Treatment of Mammary Carcinoma in The Netherlands, and while considering our own findings, we came to the conclusion that it is important to establish the number of patients required for a clinical trial.

In Chapter II a survey is given of our material and of the manner in which it was recorded and processed, while the problems encountered in statistical analysis are discussed.

The uncertainties caused by the introduction of possibly false data, and the possibility of selection caused by the inclusion or exclusion of not entirely exact recorded data is considered.

It appeared that our series of 1500 patients with mammary tumors could not be used in obtaining statistically reliable conclusions as to the value of different methods

of treatment, at which we had originally aimed, but however it appeared to be useful in estimating the number of patients required for a clinical trial.

Chapter III describes our approach in estimating the number of patients required for a clinical trial.

By using this approach it will be possible to compute:

X_{ct}: The number of patients actually included in the trial, and

X_m: The total number of patients with mammary carcinoma that must be available if the trial is to be possible.

X_p : The number of members of general female population required for it.

From these figures an investigator can also decide the possibilities of designing a clinical trial with a given series of patients. Some statistical tests are described. For a more detailed discussion of these tests the reader is referred to Part VI of the Appendix. Since the χ^2 test is generally used in trials concerning mammary carcinoma, we also used this test in our study. The examples worked out are based on the assumption that differences in result rates between two thereapies of 10%, or multiples thereof, had to be detected, and for this purpose, table S1 has been used.

Problems concerning the constitution of homogeneous groups of patients are discussed.

In our opinion it is pointless to ressort to mass registration of patients with a given disease for inclusion in a clinical trial. Only by finding the answer to clearly stated questions will it be possible to obtain data of clinical validity, and if these questions are to be answered, the material will have to meet certain requirements. Only a small proportion of the total number of patients mostly will be suitable for a study of these questions.

In the Appendix Part I, frequency tables (f_n) are given about the noticed data from our series of 1500 patients. As a clinical trial aims at forming comparable groups, these tables can be used in computing the number of patients required if all patients concerned are to meet the proposed requirements.

In using the contingency tables (f_c) for 15 characteristics of the tumor and the host, possible dependencies can be taken into account. The conceptions of McDonald, McWhirter, and Bruce on 'curative operability' are described. Further, we determined the 'curative operability' according to our criteria.

From O tables (Appendix Part II) an impression can be gained of the timing of local and/or regional recurrences and of distant metastases as recorded in our series, and a survey is also given of the time and cause of death. From these data 'the curative operability' by clinical stage is computed.

Clinical staging is stated whenever it appeared that commonly used clinical classifications show considerable differences. In order to show the degree of these differences, the classifications concerned are projected on to the International TNM classification, while at the same time we computed the stage distribution in our material in the terms of the other classification.

This comparison between clinical classifications is used as an argument against intensifying the problems of mammary carcinoma research by using noncomparable classifications. Data concerning clinical staging, needed in the formation of homogeneous groups, can be obtained from tables f_n an f_c.

Chapter IV presents the computations in the context of the organization of several imaginary clinical trials.

Our study has shown that, even with a nation-wide organization of such trials in our country, the material will not yield sufficiently large categories of patients to carry out one of these studies.

Chapter V relates our approach to a number of clinical trials already completed. The clinical trials considered almost only allow general conclusions. The division into subgroups according to characteristics that affect the prognosis gives rise to marked fragmentation of the material, and this fragmentation only permits investigations on the basis of a relatively big difference in result rates to be expected between the two therapy groups.

In case such a big difference in result rates could not be demonstrated, however, the possibility remains that there actually is a difference, but this difference will be smaller than the expected bigger difference in result rates on the basis of which the investigations concerned have been designed.

These trials should be repeated with larger numbers of patients in order to demonstrate such smaller differences.

SAMENVATTING EN CONCLUSIES

In hoofdstuk I wordt de belangrijke plaats, die 'controlled clinical trials' innemen bij het onderzoek naar de beste therapie voor de behandeling van het mammacarcinoom, beschreven.

Uit wat momenteel bekend is betreffende het verloop en de behandeling van mammacarcinoom, is niet met enige zekerheid na te gaan welke speciale therapie dient te worden gekozen voor de behandeling van een bepaalde patiënt met een bepaald mammacarcinoom. Naar onze mening geven de gevolgtrekkingen, welke kunnen worden gemaakt uit de gegevens van tot dusver uitgevoerde retrospectieve onderzoekingen betreffende de resultaten van verschillende therapieën, onvoldoende zekerheid om volledig betrouwbare richtlijnen voor de kliniek op te stellen.

Het eigen materiaal van 1500 patiënten met kwaadaardige nieuwvormingen van de borstklier is hier een voorbeeld van. Onze bevindingen maken duidelijk, dat het verzamelen van grote en goed gedocumenteerde series patiënten nog niet garandeert, dat er met behulp van dit materiaal betrouwbare conclusies kunnen worden getrokken. Het opnemen van nieuwe groepen patiënten in de serie zal dit probleem niet oplossen, want de diverse ongeselecteerde groepen patiënten zullen onderlinge, moeilijk te definiëren verschillen vertonen, zodat door het toevoegen van nieuwe groepen patiënten aan het materiaal slechts nieuwe onzekerheden worden toegevoegd.

Onderzoekingen die dit probleem oplossen zijn noodzakelijk en 'controlled clinical trials' lijken de aangewezen methode te zijn.

Een 'controlled clinical trial' is een onderzoek, waarbij twee of meer behandelingsmethoden voor een nauwkeurig omschreven ziektebeeld, worden vergeleken bij identieke groepen patiënten.

Het onderzoek is gericht op de beantwoording van een concrete vraag, en dient te voldoen aan de eisen die men stelt aan een goede statistische analyse.

Men moet zulke trials op dezelfde wijze opzetten als een laboratorium experiment. Zowel naar aanleiding van de discussies in de Commissie Mammacarcinoom van het LOK als naar aanleiding van eigen bevindingen kwamen wij tot de overtuiging, dat het belangrijk is om vast te stellen hoeveel patiënten men nodig zal hebben om een 'clinical trial' uit te kunnen voeren.

In Hoofdstuk II wordt een overzicht gegeven van het eigen materiaal en de wijze waarop dit materiaal werd geregistreerd en bewerkt, terwijl tevens de problemen die zich voordeden bij de statistische analyse worden beschreven. Ook wordt beschreven,

op welke wijze mogelijk foutieve gegevens in het geregistreerde patiëntenmateriaal terecht zijn gekomen. Daarnaast wordt de mogelijke praeselectie, veroorzaakt door het invoegen of weglaten van gegevens die niet geheel exact werden geregistreerd, beschouwd.

Hoewel het oorspronkelijk in de bedoeling lag ons materiaal van 1500 patiënten met mammatumoren te gebruiken voor een onderzoek naar het resultaat van verschillende behandelingswijzen bleek nu, dat het niet mogelijk was statistisch verantwoorde conclusies te trekken. Daarentegen bleek het wel mogelijk ons patiëntenmateriaal te gebruiken voor een schatting van het aantal patiënten dat nodig zal zijn om een 'clinical trial' uit te voeren.

In Hoofdstuk III wordt beschreven op welke wijze men het benodigde aantal patiënten voor een 'clinical trial' kan schatten.

Het is mogelijk de volgende factoren te berekenen:

X_{ct}: Het aantal patiënten dat in feite in de 'clinical trial' wordt opgenomen,

X_m: Het totale aantal patiënten met mammacarcinoom dat beschikbaar moet zijn om een 'clinical trial' mogelijk te maken, en

X_p : Het aantal leden van de gehele vrouwelijke bevolking dat beschikbaar moet zijn om de 'clinical trial' mogelijk te maken.

Wanneer een onderzoeker een bepaalde groep patiënten wil gebruiken voor een 'clinical trial', kan hij zich met behulp van de berekening oriënteren over de aard van het onderzoek, dat mogelijk is met behulp van deze groep patiënten.

Enige statistische toetsen worden beschreven. Voor een meer gedetailleerde beschrijving van deze toetsen wordt de lezer verwezen naar Deel VI van de Appendix.

Daar de χ^2 toets meestal wordt gebruikt bij trials betreffende mammacarcinoom werd deze toets ook in onze studie toegepast. De voorbeelden die werden uitgewerkt zijn er op gebaseerd dat verschillen in resultaat tussen twee therapieën van 10% of veelvouden daarvan kunnen worden ontdekt. Hiertoe werd tabel S1 gebruikt. De problemen bij het samenstellen van homogene patiëntengroepen worden besproken. Naar onze mening is het niet zinvol om bij de opzet van een 'clinical trial' over te gaan tot massale registratie van patiënten die aan een bepaalde ziekte lijden. Slechts wanneer men het antwoord op duidelijk omschreven vragen vindt, zal het mogelijk zijn bruikbare klinische gegevens te verkrijgen.

Om dergelijke vragen te kunnen beantwoorden moet het patiëntenmateriaal aan bepaalde eisen voldoen. Meestal zal slechts een klein omschreven deel van de gehele serie patiënten te gebruiken zijn voor een dergelijk onderzoek. In de Appendix Deel I worden frequentietabellen (f_n) gegeven betreffende alle exact geregistreerde gegevens uit onze serie van 1500 patiënten.

Bij het vormen van vergelijkbare patiëntengroepen voor een 'clinical trial', waarbij alle patiënten dezelfde karakteristieke eigenschappen dienen te hebben, zijn deze tabellen te gebruiken om het voor de 'trial' benodigde aantal patiënten te berekenen. Door de 'contingency' tabellen (f_c) te gebuiken, die 15 karakteristieke eigenschappen van de tumor en de gastheer betreffen, kan men mogelijke onderlinge afhankelijkheid van deze eigenschappen in de berekening betrekken.

De opvattingen van McDonald, McWhirter en Bruce betreffende de curatieve operabiliteit worden beschreven. Tevens wordt aan de hand van eigen criteria de curatieve operabiliteit bepaald. Uit de O tabellen (Appendix Deel II) kan een indruk worden verkregen over het tijdstip waarop locale en/of regionale recidieven en me-

tastasen op afstand zich manifesteren bij de patiënten van onze serie; ook wordt een overzicht gegeven betreffende tijdstip en oorzaak van overlijden. Met behulp van deze gegevens wordt de curatieve operabiliteit voor elk klinisch stadium berekend.

In §8 wordt de klinische klassificatie beschreven, omdat blijkt dat algemeen gebruikte klinische klassificaties onderling grote verschillen vertonen. Om een indruk te geven van de aard van deze verschillen worden de betreffende klassificaties geprojecteerd op de Internationale TNM klassificatie, terwijl met behulp van de computer de indeling naar stadium in het eigen materiaal werd omgewerkt volgens de eisen van de andere klassificaties. Deze vergelijking tussen enkele klinische klassificaties wordt gebruikt als argument tegen het intensiveren van de problemen rondom de research op het gebied van mammacarcinoom, veroorzaakt door het gebruik van niet vergelijkbare klassificaties. Gegevens betreffende de klinische klassificaties, die nodig zijn om homogene patiëntengroepen te vormen, kunnen worden gevonden in de f_n en f_c tabellen.

In Hoofdstuk IV wordt aan de hand van enkele denkbeeldige 'clinical trials' het daartoe benodigde aantal patiënten berekend. Uit deze berekeningen blijkt, dat zelfs een organisatie, die ons gehele land zou omvatten onvoldoende aantallen patiënten op zou leveren om een van deze 'trials' werkelijk uit te voeren.

In Hoofdstuk V wordt onze benadering toegepast op een aantal reeds voltooide 'trials'. Deze 'clinical trials' staan vrijwel alleen algemene conclusies toe. De verdeling in subgroepen, bij deze trials toegepast aan de hand van karakteristieke eigenschappen die de prognose kunnen beïnvloeden, geeft aanleiding tot een sterke opsplitsing van het patiëntenmateriaal. Deze opsplitsing laat slechts onderzoekingen toe op basis van een te verwachten relatief groot verschil in resultatenpercentages tussen de twee therapiegroepen. De mogelijkheid blijft bestaan dat, wanneer dit relatief grote verschil in resultatenpercentages niet kon worden aangetoond, er in werkelijkheid toch een verschil bestaat, maar dit verschil zal kleiner zijn dan het grotere verschil in resultatenpercentages dat werd verwacht, en op basis waarvan deze onderzoekingen werden opgezet. Men zou deze 'trials' moeten herhalen met een groter aantal patiënten, om dergelijke kleinere verschillen aan te kunnen tonen.

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APPENDIX

PART I FIGURES TO BE USED IN FORMING HOMOGENEOUS SUB-GROUPS

§ 1 *Frequency tables*

CONTENTS

TABLE f 1 *Center.*

	Tilburg	Arnhem	Leeuwarden	Totals whole series	Totals noticed data
No.	*643*	*314*	*460*	*1417*	*1417*
%	45 4	22 2	32 4		**100.0**

TABLE f 2 *Date of admission.*

	1947–1949	1950–1954	1955–1959	1960–1964	1965–1967	Other	Totals whole series	Totals noticed data
No	*41*	*161*	*372*	*684*	*157*	*2*	*1417*	*1415*
%	2 9	11 4	26 3	48 3	11 1			**100.0**

TABLE f 3 *Marital status.*

	Unmarried	Married	Religious	Other	Totals whole series	Totals noticed data
No	*204*	*1178*	*30*	*5*	*1417*	*1412*
%	14 4	83 4	2 1			**100 0**

TABLE f 4 *Duration of symptoms before starting treatment (Information obtained from patient).*

	0–13 days	14–30 days	1–2 months	3–5 months	6–11 months	1–2 years	3–4 years	5–9 years	⩾ 10 years	Other	Totals whole series	Totals noticed data
No.	*194*	*258*	*230*	*210*	*158*	*188*	*53*	*26*	*19*	*81*	*1417*	*1336*
%	14 4	19 6	17 1	15 9	11 4	14 1	3 9	2 1	1 5			**100.0**

TABLE f 5 *First consultation of family doctor (Time until onset of clinical treatment).*

	0–13 days	14–30 days	1–2 months	3–5 months	6–11 months	1–2 years	3–4 years	5–9 years	⩾ 10 years	Other	Totals whole series	Totals noticed data
No	*631*	*126*	*77*	*35*	*34*	*35*	*9*	*9*	*6*	*455*	*1417*	*962*
%	65 6	13 1	8 0	3 6	3 5	3 6	0 9	0 9	0 6			**100 0**

TABLE f 6 *First consultation of surgeon (Time until onset of clinical treatment).*

	0–13 days	14–30 days	1–2 months	3–5 months	6–11 months	1–2 years	3–4 years	5–9 years	⩾ 10 years	Other	Totals whole series	Totals noticed data
No	*827*	*64*	*35*	*8*	*10*	*10*	*4*	*5*	*4*	*450*	*1417*	*967*
%	85 5	6 6	3 6	0 8	1 0	1 0	0 4	0 5	0 4			**100 0**

TABLE f 7 *Manifestation of tumor.*

	Accidental discovery by patient	Deliberate self examination	By periodic medical examination	Accidental discovery by physician	With reference to breast complaints	With reference to other complaints	Other	Totals whole series	Totals noticed data
No.	*1161*	*24*	*2*	*94*	*38*	*22*	*76*	*1417*	*1341*
%	86 5	1 8	0 1	7 0	2 8	1 6			**100.0**

TABLE f 8 *Age at menarche.*

	< 11 years	11–16 years	> 16 years	Other	Totals whole series	Totals noticed data
No.	*9*	*784*	*74*	*550*	*1417*	*867*
%	1.0	90.4	8.5			100.0

TABLE f 9 *Duration of menstrual cycle.*

	< 3 days	3–5 days	> 5 days	Other	Totals whole series	Totals noticed data
No.	*15*	*449*	*103*	*850*	*1417*	*567*
%	2.6	79.2	18.2			100.0

TABLE f 10 *Frequency of menstrual cycle.*

	< 21 days	21–25 days	26–30 days	> 30 days	Other	Totals whole series	Totals noticed data
No.	*5*	*62*	*504*	*18*	*828*	*1417*	*589*
%	0.8	10.5	85.6	3.1			100.0

TABLE f 11 *Regularity of menstrual cycle.*

	Regular	Irregular	Other	Totals whole series	Totals noticed data
No.	*506*	*97*	*814*	*1417*	*603*
%	83.8	16.2			100.0

TABLE f 12 *Occurrence of mastopathia (Anamnesis).*

	No mastopathia	Mastopathia	Other	Totals whole series	Totals noticed data
No.	*348*	*37*	*1032*	*1417*	*385*
%	90.4	9.6			100.0

TABLE f 13 *Incidence of carcinoma in the family.*

	One case of breast cancer in the family	More than one case of breast cancer in the family	One case of other carcinoma in the family	More than one case of other carcinoma in the family	Breast cancer and other carcinoma in the family	No carcinoma in the family	Other	Totals whole series	Totals noticed data
No.	*43*	*6*	*95*	*26*	*16*	*410*	*821*	*1417*	*596*
%	7.2	1.0	15.9	4.4	2.7	68.8			100.0

TABLE f 14 *Numbers of marriages.*

	1 marriage	2 marriages	3 marriages	Unmarried	Other	Totals whole series	Totals noticed data
No.	*1149*	*27*	*2*	*234*	*5*	*1417*	*1412*
%	81.4	1.9	0.1	16.5			100.0

TABLE f 15 *Age (10 year periods).*

	< 20 years	20–29 years	30–39 years	40–49 years	50–59 years	60–69 years	70–79 years	80–89 years	Other	Totals whole series	Totals noticed data
No.	*4*	*13*	*92*	*327*	*360*	*322*	*223*	*74*	*2*	*1417*	*1415*
%	0.3	0.9	6.5	23.1	24.5	22.8	15.8	5.2			100.0

TABLE f 16 *Age (3 age groups).*

	< 35 years	35–49 years	50–69 years	> 69 years	Other	Totals whole series	Totals noticed data
No	*42*	*394*	*682*	*297*	*2*	*1417*	*1415*
%	3 0	27 8	48 2	21 0			100 0

TABLE f 17 *Puerperal mastitis.*

	Left side	Right side	Both sides	No puerperal mastitis	Other	Totals whole series	Totals noticed data
No	*32*	*17*	*6*	*951*	*411*	*1417*	*1006*
%	3 2	1 7	0 6	94 5			100.0

TABLE f 18 *Numbers of abortions.*

	1 abortion	2 abortions	⩾ 3 abortions	No abortion	Other	Totals whole series	Totals noticed data
No	*134*	*56*	*35*	*852*	*340*	*1417*	*1077*
%	12 4	5 2	3 2	79 2			100 0

TABLE f 19 *Age at onset of menopause (5 year periods).*

	< 35 years	35 39 years	40–44 years	45–49 years	50–54 years	55–59 years	⩾ 60 years	No menopause	Other	Totals whole series	Totals noticed data
No	*6*	*25*	*84*	*206*	*323*	*35*	*2*	*225*	*511*	*1417*	*906*
%	0 7	2 8	9 3	22 7	35 7	3 9	0 2	24 8			100,0

TABLE f 20 *Age at onset of menopause (3 age groups).*

	< 45 years	45–55 years	⩾ 55 years	No menopause	Other	Totals whole series	Totals noticed data
No	*115*	*529*	*37*	*225*	*511*	*1417*	*906*
%	12 7	58 4	4 1	24 8			100 0

TABLE f 21 *Cause of menopause.*

	Spontaneous	Surgical or radiological castration	No menopause	Other	Totals whole series	Totals noticed data
No	*616*	*69*	*225*	*507*	*1417*	*910*
%	67 7	7 6	24 7			100 0

TABLE f 22 *Clinical manifestation of tumor.*

	Occult tumor	Tumor manifest	Other	Totals whole series	Totals noticed data
No	*19*	*1326*	*72*	*1417*	*1345*
%	1 4	98 6			100 0

TABLE f 23 *Site of tumor.*

	Right	Left	Other	Totals whole series	Totals noticed data
No	*686*	*717*	*14*	*1417*	*1403*
%	48 9	51 1			100 0

TABLE f 24 *Location of tumor (in detail).*

	Upper half	Lower half	Inner half	Outer half	Upper outer quadrant	Lower outer quadrant	Upper inner quadrant	Lower inner quadrant	Central	Whole breast	Other	Totals whole series	Totals noticed data
No.	*158*	*52*	*48*	*156*	*373*	*72*	*127*	*43*	*237*	*69*	*82*	*1417*	*1335*
%	12.0	3.9	3.6	11.7	27.8	5.4	9.5	3.3	17.7	5.1			**100.0**

TABLE f 25 *Location of tumor (medial, lateral).*

	Medial, subareolar or whole breast	Lateral	Other	Totals whole series	Totals noticed data
No.	*734*	*601*	*82*	*1417*	*1935*
%	55.0	45.0			**100.0**

TABLE f 26 *Size of tumor.*

Symbols International TNM classification	T1	T2	T3	T4			
Symptoms	Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
No.	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
%	15.1	44.1	33.3	7.5			**100.0**

TABLE f 27 *Fixation to skin.*

Symbols International TNM classification	T1	T2	T3	T4			
Symptoms	Skin not involved	Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Other	Totals whole series	Totals noticed data
No.	*581*	*349*	*344*	*84*	*59*	*1417*	*1358*
%	42.7	25.7	25.4	6.2			**100.0**

TABLE f 28 *Paget's disease of the nipple.*

Symbols International TNM classification		T1	T2			
Symptoms	No Paget's disease	Limited to the nipple	Outside the nipple	Other	Totals whole series	Totals noticed data
No.	*1299*	*20*	*14*	*84*	*1417*	*1333*
%	97.4	1.5	1.1			**100.0**

TABLE f 29 *Nipple retraction.*

Symbols International TNM classification		T2			
Symptoms	No nipple retraction	Nipple retraction	Other	Totals whole series	Totals noticed data
No.	*933*	*398*	*86*	*1417*	*1331*
%	70 1	29 9			**100.0**

TABLE f 30 *Pectoral muscle fixation.*

Symbols International TNM classification	T1	T3a	T3b			
Symptoms	No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
No	*1058*	*168*	*92*	*99*	*1417*	*1318*
%	80 3	12 7	7.0			**100.0**

TABLE f 31 *Chest wall attachment.*

Symbols International TNM classification	T1	T4			
Symptoms	Not fixed	Fixed	Other	Totals whole series	Totals noticed data
No	*1297*	*19*	*101*	*1417*	*1316*
%	98 5	1 4			**100.0**

TABLE f 32 *Status of the homolateral axillary lymph nodes.**

Symbols International TNM classification	N0	N1a	N1x	N1y	N2a	N2b			
Symptoms	No lymph nodes palpable	Considered to contain no growth	Single	Multiple	Fixed to one another	Fixed to other structures	Other	Totals whole series	Totals noticed data
No	*744*	*89*	*242*	*208*	*35*	*58*	*41*	*1417*	*1376*
%	54 1	61 5	17 6	15.1	2 5	4 2			**100.0**

* In f_c tables N 0 and N1a are headed under 'considered to contain no growth', N2a and N2b under 'fixed to one another or to other structures'

TABLE f 33 *Status of the supra- and infraclavicular lymph nodes.**

Symbols International TNM classification	N3	N0		
Symptoms	Considered to contain growth	Other	Totals whole series	Totals noticed data
No.	*80*	*1337*	*1417*	*80*
%	100 0			**100.0**

* 'Considered to contain no growth' and 'unknown' both are headed under 'Other'.

TABLE f 34 *Arm edema.*

Symbols International TNM classification	N3	N0		
Symptoms	Arm edema	Other	Totals whole series	Totals noticed data
No.	*44*	*1373*	*1417*	*44*
%	100.0			**100.0**

TABLE f 35 *Clinical stage (International* TNM *classification).*

	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
No.	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
%	29.4	13.0	52.8	4.9			**100.0**

TABLE f 36 *Clinical stage (International* TNM *classification).*
Stage III *is divided into two groups, a: large tumor only, no other symptoms*; b: also other symptoms.*

	Stage I	Stage II	Stage III, large tumor only, no other symptoms	Stage III, also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
No.	*414*	*183*	*184*	*559*	*69*	*8*	*1417*	*1409*
%	29.4	13.0	13.1	39.7	4.9			**100.0**

Stage IIIa including:
T1 or T2 (Skin, Paget's disease, Nipple retraction, Pectoral muscle fixation, Chest wall attachment)
T3 (Size) N0 M0
T3 (Size) NI M0

TABLE f 37 *Interval between biopsy and surgical treatment.*

	0–1 day	2–14 days	15 days or more	Other	Totals whole series	Totals noticed data
No.	*444*	*659*	*268*	*46*	*1417*	*1371*
%	32.4	48.0	19 6			**100.0**

TABLE f 38 *Contents of tumor in cm³ (Pathological report).**

	< 1 cm³	1–5 cm³	6–10 cm³	11–20 cm³	21–30 cm³	31–50 cm³	51–100 cm³	101–200 cm³	201–500 cm³	501–1000 cm³	More than 1000 cm³	Other	Totals whole series	Totals noticed data
No.	*20*	*106*	*209*	*88*	*146*	*54*	*73*	*47*	*34*	*11*	*15*	*614*	*1417*	*803*
%	2.5	13.2	26.0	10.9	18.2	6.7	9.3	5 8	4.2	1.3	1.9			**100.0**

* Calculated from reported diameters.

TABLE f 39 *Largest diameter of tumor (Pathological report).*

	< 1 cm	1 cm	2 cm	3 cm	4 cm	5 cm	6 cm	7 cm	8 cm	Other	Totals whole series	Totals noticed data
No.	*23*	*44*	*252*	*248*	*93*	*80*	*44*	*47*	*46*	*540*	*1417*	*877*
%	2 6	5.0	28.7	28.3	10.6	9.1	5.0	5.4	5.2			**100.0**

TABLE f 40 *Microscopic infiltration of skin (Pathological report).*

	Scanty infiltration	Extensive infiltration	Ulceration	No infiltration	Other	Totals whole series	Totals noticed data
No.	*17*	*170*	*26*	*476*	*728*	*1417*	*689*
%	2 5	24 7	3 8	69 1			**100.0**

TABLE f 41 *Microscopic infiltration of mammary tissue (Pathological report).*

	Scanty infiltration	Extensive infiltration	No infiltration	Other	Totals whole series	Total noticed data
No	*29*	*282*	*195*	*911*	*1417*	*506*
%	5 7	55 7	38 5			**100.0**

TABLE f 42 *Microscopic infiltration of fatty tissue (Pathological report).*

	Scanty infiltration	Extensive infiltration	No infiltration	Other	Totals whole series	Totals noticed data
No	*51*	*276*	*140*	*950*	*1417*	*467*
%	10 9	59 1	30 0			**100.0**

TABLE f 43 *Microscopic infiltration of muscle (Pathological report).*

	Scanty infiltration	Extensive infiltration	No infiltration	Other	Totals whole series	Totals noticed data
No	*8*	*67*	*583*	*759*	*1417*	*658*
%	1 2	10 2	88 6			**100 0**

TABLE f 44 *Microscopic infiltration of blood vessels (Pathological report).*

	Scanty infiltration	Extensive infiltration	No infiltration	Other	Totals whole series	Totals noticed data
No	*19*	*68*	*270*	*1060*	*1417*	*357*
%	5 3	19 0	75 6			**100.0**

TABLE f 45 *Microscopic structure of tumor (Pathological report).*

	Single fields of cells	Single fields of cells and solid buds of cells	Single fields of cells, solid buds of cells and duct formation	Single fields of cells, solid buds of cells and papillary structures	Single fields of cells, duct formation and cystic papillary	Cell masses, duct formation and papillary structures	Solitary cells, cell masses and duct formation	Duct formation	Cystic papillary	Papillary structures	Other	Totals whole series	Totals noticed data
No	*1*	*293*	*141*	*1*	*3*	*1*	*1*	*56*	*3*	*27*	*890*	*1417*	*527*
%	0 2	55 6	26 8	0 2	0 6	0 2	0 2	10 6	0 6	5 1			**100.0**

TABLE f 46 *Ducts (Pathological report).*

	Tumor-growth in ducts	Duct papilloma	Invasive growth	Other	Totals whole series	Totals noticed data
No.	*166*	*27*	*20*	*1204*	*1417*	*213*
%	77 9	12 7	9 4			**100.0**

TABLE f 47 *Characteristics of the nucleus (Pathological report).*

	Round	Round and spindle	Round, spindle and polymorph	Round and atype	Round, polymorph and vacuolisation	Vesicular	Polymorph	Polymorph and vacuolisation	Hyperchromatic	Other	Totals whole series	Totals noticed data
No	*1*	*6*	*3*	*1*	*1*	*33*	*118*	*4*	*17*	*1233*	*1417*	*184*
%	0 5	3 3	1 6	0 5	0 5	17 9	64 3	2 2	9 2			**100 0**

TABLE f 48 *Fibrous stroma formation (Pathological report).*

	Scarce fibrous stroma infiltration	Abundant fibrous stroma infiltration	Other	Totals whole series	Totals noticed data
No	*34*	*404*	*979*	*1417*	*438*
%	7 8	92 2			**100.0**

TABLE f 49 *Histology of the axillary lymph nodes (Pathological report).*

	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
No.	*402*	*652*	*363*	*1417*	*1054*
%	38 1	61 9			**100 0**

TABLE f 50 *Pathological Diagnosis.*

	Solid carcinoma	Colloid carcinoma	Medullary carcinoma	Intraductal carcinoma (Comedo carcinoma)	Papillary carcinoma	Paget's disease	Inflammatory carcinoma	Carcinoma, non specified	Other	Totals whole series	Totals noticed data
No.	*826*	*38*	*38*	*258*	*11*	*16*	*5*	*225*	—	*1417*	*1417*
%	58 5	2.7	2 7	18 4	0 7	1 1	0.4	15.5			**100.0**

CONTENTS

	Marital status	Age	Duration of symptoms	Age at onset of menopause	Cause of menopause	Location of tumor
Marital status		f_c1	f_c2	f_c3	f_c4	f_c5
Age	f_c1		f_c14	f_c15	f_c16	f_c17
Duration of symptoms	f_c2	f_c14		f_c27	f_c28	f_c29
Age at onset of menopause	f_c3	f_c15	f_c27		f_c39	f_c40
Cause of menopause	f_c4	f_c16	f_c28	f_c39		f_c49
Location of tumor	f_c5	f_c17	f_c29	f_c40	f_c49	
Size of tumor	f_c6	f_c18	f_c30	f_c41	f_c50	f_c58
Fixation to skin	f_c7	f_c19	f_c31	f_c42	f_c51	f_c59
Nipple retraction	f_c8	f_c20	f_c32	f_c43	f_c52	f_c60
Pectoral muscle fixation	f_c9	f_c21	f_c33	f_c44	f_c53	f_c61
Status of the homolateral axillary lymph nodes	f_c10	f_c22	f_c34	f_c45	f_c54	f_c62
Status of the supra- and infraclavicular lymph nodes	f_c11	f_c23	f_c35	f_c46	f_c55	f_c63
Clinical staging (International TNM classification)	f_c12	f_c24	f_c36	f_c47	f_c56	f_c64
Clinical staging (International TNM classification) Stage III is divided		f_c25	f_c37			f_c65
Histology of the axillary lymph nodes	f_c13	f_c26	f_c38	f_c48	f_c57	f_c66

Size of tumor	Fixation to skin	Nipple retraction	Pectoral muscle fixation	Status of the homolateral axillary lymph nodes	Status of the supra- and infraclavicular lymph nodes	Clinical staging (International TNM classification)	Clinical staging (International TNM classification) Stage III is divided	Histology of the axillary lymph nodes
f_c6	f_c7	f_c8	f_c9	f_c10	f_c11	f_c12		f_c13
f_c18	f_c19	f_c20	f_c21	f_c22	f_c23	f_c24	f_c25	f_c26
f_c30	f_c31	f_c32	f_c33	f_c34	f_c35	f_c36	f_c37	f_c38
f_c41	f_c42	f_c43	f_c44	f_c45	f_c46	f_c47		f_c48
f_c50	f_c51	f_c52	f_c53	f_c54	f_c55	f_c56		f_c57
f_c58	f_c59	f_c60	f_c61	f_c62	f_c63	f_c64	f_c65	f_c66
	f_c67	f_c68	f_c69	f_c70	f_c71	f_c72		f_c73
f_c67		f_c74	f_c75	f_c76	f_c77	f_c78	f_c79	f_c80
f_c68	f_c74		f_c81	f_c82	f_c83	f_c84	f_c85	f_c86
f_c69	f_c75	f_c81		f_c87	f_c88	f_c89		f_c90
f_c70	f_c76	f_c82	f_c87		f_c91	f_c92	f_c93	f_c94
f_c71	f_c77	f_c83	f_c88	f_c91		f_c95	f_c96	f_c97
f_c72	f_c78	f_c84	f_c89	f_c92	f_c95			f_c98
	f_c79	f_c85		f_c93	f_c96			f_c99
f_c73	f_c80	f_c86	f_c90	f_c94	f_c97	f_c98	f_c99	

	Marital status	Age: < 35 years	35–49 years	50–69 years	> 69 years	Totals noticed data
Numbers	Unmarried	*6*	*60*	*105*	*63*	*234*
		2 6	25 6	44 9	26 9	100.0
		14 3	15 2	15 5	21 2	16 6
		0 4	4 3	7 4	4 5	16 6
Numbers	Married	*36*	*334*	*573*	*234*	*1177*
		3 1	28 4	48 7	19 9	100.0
		85 7	84 8	84 5	78 8	83 4
		2 6	23 7	40 6	16 6	83 4
Numbers	Totals noticed data	*42*	*394*	*678*	*297*	*1411*
		3 0	27 9	48 1	21 0	100.0
		100.0	100 0	100.0	100 0	100.0
		3 0	27 9	48 1	21 0	100.0

	Marital status	Age: < 35 years	35–49 years	50–69 years	> 69 years	Totals noticed data
	Unmarried	*6*	*60*	*105*	*63*	*234*
% Horizontal		2 6	25 6	44 9	26 9	100.0
% Vertical		14 3	15 2	15 5	21 2	16 6
		0 4	4 3	7 4	4 5	16 6
	Married	*36*	*334*	*573*	*234*	*1177*
% Horizontal		3 1	28 4	48 7	19 9	100.0
% Vertical		85 7	84 8	84 5	78 8	83 4
		2 6	23 7	40 6	16 6	83 4
	Totals noticed data	*42*	*394*	*678*	*297*	*1411*
% Horizontal		3 0	27 9	48 1	21 0	100 0
% Vertical		100.0	100.0	100.0	100.0	100 0
		3 0	27 9	48 1	21 0	100 0

Marital status	Age < 35 years	35–49 years	50–69 years	> 69 years	Totals noticed data
Unmarried	*6*	*60*	*105*	*63*	*234*
	2.6	25.6	44.9	26.9	100.0
	14.3	15.2	15.5	21.2	16.6
	0.4	4.3	7.4	4.5	16.6
Married	*36*	*334*	*573*	*234*	*1177*
	3.1	28.4	48.7	19.9	100.0
	85.7	84.8	84.5	78.8	83.4
	2.6	23.7	40.6	16.6	83.4
Totals noticed data	*42*	*394*	*678*	*297*	*1411*
	3.0	27.9	48.1	21.0	100.0
	100.0	100.0	100.0	100.0	100.0
	3.0	27.9	48.1	21.0	= 100.0

% Totals noticed data

EXPLANATION OF TWO-WAY CONTINGENCY TABLES (f_c)

Totals whole series = Absolute figures including 'knowns 'and 'unknowns' of whole series.

Totals noticed data = Absolute figures of the number of 'knowns', the relative frequencies are calculated only for the 'knowns'.

Other = Absolute figures of the number of 'unknowns'.

Per datum four figures are given:

First figure= the absolute figure *(italics)*.

Second figure = Percentage of row totals (% Horizontal); totals noticed data of row concerned considered as 100%.

Third figure = Percentage of column totals (% Vertical); totals noticed data of column concerned considered as 100%.

Fourth figure = Percentage of table totals (% Totals noticed data); totals noticed data of whole material considered as 100%.

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 1 *Marital status* versus *Age.*

Marital status	Age						
	< 35 years	35–49 years	50–69 years	> 69 years	Other	Totals whole series	Totals noticed data
Unmarried	*6*	*60*	*105*	*63*	–	*234*	*234*
	2 6	25 6	44 9	26 9			100.0
	14 3	15 2	15 5	21 2			16 6
	0 4	4 3	7 4	4 5			16 6
Married	*36*	*334*	*573*	*234*	*1*	*1178*	*1177*
	3 1	28 4	48 7	19 9			100 0
	85 7	84 8	84 5	78 8			83 4
	2 6	23 7	40 6	16 6			83 4
Other	–	–	*4*	–	*1*	*5*	–
Totals whole series	*42*	*394*	*682*	*297*	*2*	*1417*	*1415*
Totals noticed data	*42*	*394*	*678*	*297*	–	*1412*	*1411*
	3 0	27 9	48 1	21 0			100 0
	100 0	100 0	100 0	100.0			100.0
	3 0	27 9	48 1	21 0			100 0

TABLE f_c 2 *Marital status* versus *Duration of symptoms.*

Marital status	Duration of symptoms before starting treatment					
	0–30 days	1–6 months	> 6 months	Other	Totals whole series	Totals noticed data
Unmarried	*77*	*66*	*74*	*17*	*234*	*217*
	35 5	30 4	34 1			100.0
	17 1	15 0	16 7			16 3
	5 8	5 0	5 6			16 3
Married	*374*	*373*	*368*	*63*	*1178*	*1115*
	33 5	33 5	33 0			100.0
	82 9	85 0	83 3			83 7
	28 1	28 0	27 6			83 7
Other	*1*	*1*	*2*	*1*	*5*	–
Totals whole series	*452*	*440*	*444*	*81*	*1417*	*1336*
Totals noticed data	*451*	*439*	*442*	–	*1412*	*1332*
	33 9	33 0	33 2			100.0
	100.0	100 0	100 0			100.0
	33 9	33 0	33 2			100 0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 3 *Marital status* versus *Age at onset of menopause.*

Marital status	Age at onset of menopause						
	< 45 years	45–55 years	> 55 years	No menopause	Other	Totals whole series	Totals noticed data
Unmarried	*16*	*88*	*5*	*28*	*97*	*234*	*137*
	11 7	64 2	3 6	20 4			100 0
	13 9	16 7	13 5	12 4			15 2
	1 8	9 7	0 6	3 1			15 2
Married	*99*	*439*	*32*	*197*	*411*	*1178*	*767*
	12 9	57 2	4 2	25 7			100.0
	86 1	83 3	86 5	87 6			84 8
	11 0	48 6	3 5	21 8			84 8
Other	–	*2*	–	–	*3*	*5*	–
Totals whole series	*115*	*529*	*37*	*225*	*511*	*1417*	*906*
Totals noticed data	*115*	*527*	*37*	*225*	–	*1412*	*904*
	12 7	58 3	4 1	24 9			100 0
	100 0	100.0	100 0	100.0			100.0
	12 7	58 3	4 1	24 9			100.0

TABLE f_c 4 *Marital status* versus *Cause of menopause.*

Marital status	Cause of menopause					
	Spontaneous	Surgical or radiological castration	No menopause	Other	Totals whole series	Totals noticed data
Unmarried	*101*	*9*	*28*	*96*	*234*	*138*
	73 2	6 5	20 3			100 0
	16 5	13 0	12 4			15 2
	11 1	1 0	3 1			15 2
Married	*512*	*60*	*197*	*409*	*1178*	*769*
	66 6	7 8	25 6			100 0
	83 5	87 0	87 6			84 8
	56 4	6 6	21 7			84 8
Other	*3*	–	–	*2*	*5*	–
Totals whole series	*616*	*69*	*225*	*507*	*1417*	*910*
Totals noticed data	*613*	*69*	*225*	–	*1412*	*907*
	67 6	7 6	24 8			100 0
	100.0	100.0	100.0			100 0
	67 6	7 6	24 8			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 5 *Marital status* versus *Location of tumor.*

	Location of tumor				
Marital status	Medial, subareolar, or whole breast	Lateral	Other	Totals whole series	Totals noticed data
Unmarried	*122*	*93*	*19*	*234*	*215*
	56.7	43.3			**100.0**
	16.7	15.5			16.2
	9.2	7.0			16.2
Married	*610*	*506*	*62*	*1178*	*1116*
	54.7	45.3			**100.0**
	83.3	84.5			83.8
	45.8	38.0			83.8
Other	*2*	*2*	*1*	*5*	–
Totals whole series	*734*	*601*	*82*	*1417*	*1335*
Totals noticed data	*732*	*599*	–	*1412*	*1331*
	55.0	45.0			**100.0**
	100.0	**100.0**			**100.0**
	55.0	45.0			**100.0**

TABLE f_c 6 *Marital status* versus *Size of tumor.*

	Size of tumor						
Marital status	Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
Unmarried	*25*	*94*	*74*	*25*	*16*	*234*	*218*
	11.5	43.1	33.9	11.5			**100.0**
	12.5	15.9	16.8	25.0			16.4
	1.9	7.0	5.6	1.9			16.4
Married	*175*	*497*	*367*	*75*	*64*	*1178*	*1114*
	15.7	44.6	32.9	6.7			**100.0**
	87.5	84.1	83.2	75.0			83.6
	13.1	37.3	27.6	5.6			83.6
Other	–	–	*4*	–	*1*	*5*	–
Totals whole series	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
Totals noticed data	*200*	*591*	*441*	*100*	–	*1412*	*1332*
	15.0	44.4	33.1	7.5			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	15.0	44.4	33.1	7.5			**100.0**

TABLE f_c 7 *Marital status* versus *Fixation to skin.*

Numbers
% Horizontal
% Vertical
% Totals noticed daat

	Fixation to skin						
Marital status	Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
Unmarried	*64*	*61*	*18*	*80*	*11*	*234*	*223*
	28.7	27.4	8.1	35.8			100.0
	18.4	17.9	21.4	13.4			16.5
	4.7	4.5	1.3	6.0			16.5
Married	*284*	*279*	*66*	*501*	*48*	*1178*	*1130*
	25.1	24.7	5.8	44.3			100.0
	81.6	82.1	78.6	86.6			83.5
	21.0	20.6	4.9	37.0			83.5
Other	*1*	*4*	–	–	–	*5*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*348*	*340*	*84*	*581*	–	*1412*	*1353*
	25.7	25.1	6.2	43.0			100.0
	100.0	100.0	100.0	100.0			100.0
	25.7	25.1	6.2	43.0			100.0

TABLE f_c 8 *Marital status* versus *Nipple retraction.*

	Nipple retraction				
Marital status	Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
Unmarried	*76*	*144*	*14*	*234*	*220*
	34.5	65.5			100.0
	19.3	15.5			16.6
	5.7	10.9			16.6
Married	*318*	*788*	*72*	*1178*	*1106*
	28.8	71.2			100.0
	80.7	84.5			83.4
	24.0	59.4			83.4
Other	*4*	*1*	–	*5*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*394*	*932*	–	*1412*	*1326*
	29.7	70.3			100.0
	100.0	100.0			100.0
	29.7	70.3			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 9 *Marital status* versus *Pectoral muscle fixation.*

	Pectoral muscle fixation					
Marital status	No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
Unmarried	*172*	*27*	*15*	*20*	*234*	*214*
	80 4	12 6	7 0			100 0
	16 3	16 2	16 5			16 3
	13 1	2 1	1 1			16 3
Married	*883*	*140*	*76*	*79*	*1178*	*1099*
	80.3	12 7	6 9			100 0
	83 7	83 8	83 5			83 7
	67 3	10 7	5 8			83 7
Other	*3*	*1*	*1*	–	*5*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*1055*	*167*	*91*	–	*1412*	*1313*
	80 4	12 7	6 9			100 0
	100.0	100.0	100.0			100.0
	80 4	12 7	6 9			100 0

TABLE f_c 10 *Marital status* versus *Status of the homolateral axillary lymph nodes.*

	Status of the homolateral axillary lymph nodes						
Marital status	Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
Unmarried	*48*	*40*	*13*	*129*	*4*	*234*	*230*
	20 9	17 4	5 7	56 0			100 0
	19 9	19 3	14 1	15 4			16 8
	3 5	2 9	0 9	9 4			16 8
Married	*193*	*167*	*79*	*702*	*37*	*1178*	*1141*
	16 9	14 6	6 9	61 5			100.0
	80 1	80 7	85 9	84 6			83 2
	14 1	12 2	5 8	51 2			83 2
Other	*1*	*1*	*1*	*2*	–	*5*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*241*	*207*	*92*	*831*	–	*1412*	*1371*
	17 6	15 1	6 7	60 6			100.0
	100.0	100.0	100.0	100 0			100.0
	17 6	15 1	6 7	60 6			100 0

TABLE fc 11 *Marital status* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Marital status	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
Unmarried	*12*	*222*	*234*	*12*
	100.0			**100.0**
	15.0			15.0
	15.0			15.0
Married	*68*	*1110*	*1178*	*68*
	100.0			**100.0**
	85.0			85.0
	85 0			85.0
Other	–	*5*	*5*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*80*	–	*1412*	*80*
	100.0			**100.0**
	100.0			**100.0**
	100.0			**100.0**

TABLE fc 12 *Marital status* versus *Clinical stage (International* TNM *classification).*

Marital status	Clinical stage (International TNM classification): Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Unmarried	*61*	*33*	*120*	*18*	*2*	*234*	*232*
	26.3	14.2	51.7	7.8			**100.0**
	14.7	18.1	16.2	26.5			16.6
	4.2	2.4	8.5	1.5			16.6
Married	*353*	*149*	*620*	*50*	*6*	*1178*	*1172*
	30.2	12.6	52.9	4.3			**100.0**
	85.3	81.9	83.8	73.5			83.4
	25.1	10.8	43 9	3 6			83.4
Other	–	*1*	*3*	*1*	–	*5*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*414*	*182*	*740*	*68*	–	*1412*	*1404*
	29.3	13.2	52.4	5.1			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	29.3	13.2	52.4	5.1			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 13 *Marital status* versus *Histology of the axillary lymph nodes.*

	Histology of the axillary lymph nodes				
Marital status	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Unmarried	*65*	*99*	*70*	*234*	*164*
	39 6	60 4			**100.0**
	16 3	15 2			15 6
	6 2	9 4			15 6
Married	*334*	*552*	*292*	*1178*	*886*
	37 7	62 3			**100.0**
	83 7	84 8			84 4
	31 8	52 6			84 4
Other	*3*	*1*	*1*	*5*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*399*	*651*	–	*1412*	*1050*
	38 0	62 0			**100 0**
	100.0	**100.0**			**100.0**
	38 0	62 0			**100.0**

TABLE f_c 14 *Age* versus *Duration of symptoms before starting treatment.*

	Duration of symptoms before starting treatment					
Age	0–30 days	1–6 months	> 6 months	Other	Totals whole series	Totals noticed data
< 35 years	*10*	*17*	*12*	*3*	*42*	*39*
	25 6	43 6	30 8			**100.0**
	2 2	3 9	2 7			2 9
	0 7	1 3	0 9			2 9
35–49 years	*132*	*137*	*112*	*13*	*394*	*381*
	34 6	36 0	29 4			**100.0**
	29 2	31 1	25 3			28 5
	9 9	10 3	8 4			28 5
50–69 years	*227*	*213*	*209*	*33*	*682*	*649*
	35 0	32 8	32 2			**100.0**
	50 2	48 4	47 2			48 6
	17 0	16 0	15 7			48 6
> 69 years	*83*	*73*	*110*	*31*	*297*	*266*
	31 2	27.4	41 4			**100.0**
	18 4	16 6	24 8			19 9
	6 2	5 5	8 2			19 9
Other	–	–	*1*	*1*	*2*	–
Totals whole series	*452*	*440*	*444*	*81*	*1417*	*1336*
Totals noticed data	*452*	*440*	*443*	–	*1415*	*1335*
	33.9	33 0	33 2			**100.0**
	100.0	**100.0**	**100.0**			**100.0**
	33 9	33 0	33 2			**100 0**

TABLE f_c 15 *Age* versus *Age at onset of menopause.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Age	Age at onset of menopause						
	< 45 years	45–55 years	> 55 years	No menopause	Other	Totals whole series	Totals noticed data
< 35 years	–	–	–	*19*	*23*	*42*	*19*
				100.0			**100.0**
				8.4			2.1
				2.1			2.1
35–49 years	*17*	*23*	–	*170*	*184*	*394*	*210*
	8.1	11.0		8.0			**100.0**
	14.8	4.4		75.6			23.2
	1.9	2.5		18.7			23.2
50–69 years	*70*	*350*	*31*	*36*	*195*	*682*	*487*
	14.4	71.9	6.4	7.4			**100.0**
	60.9	66.6	83.8	16.0			53.9
	7.7	38.7	3.4	4.0			53.9
> 69 years	*28*	*153*	*7*	–	*109*	*297*	*188*
	14.9	81.4	3.8				**100.0**
	24.3	29.0	16.2				20.8
	3.1	16.9	0.7				20.8
Other	–	*2*	–	–	–	*2*	–
Totals whole series	*115*	*528*	*38*	*225*	*511*	*1417*	*906*
Totals noticed data	*115*	*526*	*38*	*225*	–	*1415*	*904*
	12.7	58.3	4.1	24.9			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	12.7	58.3	4.1	24.9			**100.0**

TABLE f_c 16 *Age* versus *Cause of menopause.*

Age	Cause of menopause					
	Spontaneous	Surgical or radiological castration	No menopause	Other	Totals whole series	Totals noticed data
< 35 years	–	–	*20*	*22*	*42*	*20*
			100.0			**100.0**
			8.0			2.2
			2.2			2.2
35–49 years	*32*	*15*	*168*	*179*	*394*	*215*
	14.9	7.0	78.1			**100.0**
	5.2	21.7	76.0			23.7
	3.5	1.7	18.5			23.7
50–69 years	*396*	*46*	*36*	*204*	*682*	*478*
	82.8	9.6	7.5			**100.0**
	64.7	66.7	16.0			52.6
	43.7	5.1	4.0			52.6
> 69 years	*184*	*11*	–	*102*	*297*	*195*
	94.4	5.6				**100.0**
	30.0	11.6				21.5
	20.3	0.9				21.5
Other	*2*	–	–	–	*2*	–
Totals whole series	*614*	*72*	*224*	*507*	*1417*	*910*
Totals noticed data	*612*	*72*	*224*	–	*1415*	*908*
	67.6	7.6	24.8			**100.0**
	100.0	**100.0**	**100.0**			**100.0**
	67.6	7.6	24.8			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 17 *Age* versus *Location of tumor.*

Age	Location of tumor: Medial, subareolar, or whole breast	Lateral	Other	Totals whole series	Totals noticed data
< 35 years	*19*	*21*	*2*	*42*	*40*
	47.5	52 5			**100.0**
	2.6	3.5			3.0
	1.4	1.6			3.0
35–49 years	*192*	*174*	*28*	*394*	*366*
	52.5	47.5			**100.0**
	26.2	29.0			27.5
	14.4	13.1			27.5
50–69 years	*348*	*298*	*36*	*682*	*646*
	53 9	46.1			**100.0**
	47.4	49.7			48.5
	26.1	22.4			48.5
> 69 years	*175*	*106*	*16*	*297*	*281*
	62.3	37.7			**100.0**
	23.8	17.7			21.1
	13.1	8.0			21.1
Other	–	*2*	–	*2*	–
Totals whole series	*734*	*601*	*82*	*1417*	*1335*
Totals noticed data	*734*	*599*	–	*1415*	*1333*
	55.1	44.9			**100.0**
	100.0	**100.0**			**100.0**
	55.1	44 9			**100.0**

TABLE fc 18 *Age* versus *Size of tumor.*

Age	Size of tumor: Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
< 35 years	*9*	*10*	*19*	*3*	*1*	*42*	*41*
	22.0	24.4	46.3	7.3			**100.0**
	4.5	1.7	4.3	3.0			3.1
	0.7	0.7	1.4	0.2			3.1
35–49 years	*71*	*156*	*117*	*24*	*26*	*394*	*368*
	19.3	42.4	31.8	6.5			**100.0**
	35.7	26.4	26.4	24.0			27.6
	5.3	11.7	8.8	1.8			27.6
50–69 years	*83*	*295*	*216*	*45*	*43*	*682*	*639*
	13.0	46.2	33.8	7.0			**100.0**
	41.7	49.9	48.6	45.0			47.9
	6.2	22.1	16.2	3.4			47.9
> 69 years	*36*	*130*	*92*	*28*	*11*	*297*	*286*
	12.6	45.5	32.2	9.8			**100.0**
	18.1	22.0	20.7	28.0			21.4
	2.7	9.7	6.9	2.1			21.4
Other	*1*	–	*1*	–	–	*2*	–
Totals whole series	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
Totals noticed data	*199*	*591*	*444*	*100*	–	*1415*	*1334*
	14.9	44.3	33.3	7.5			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	14.9	44.3	33.3	7.5			**100.0**

TABLE f_c 19 *Age* versus *Fixation to skin.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Fixation to skin						
Age	Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
< 35 years	*7*	*7*	*1*	*22*	*5*	*42*	*37*
	18 9	18 9	2 7	59 4			**100.0**
	2 0	2 0	1 2	3 6			2 7
	0 5	0 5	0 1	1 7			2 7
35–49 years	*82*	*70*	*12*	*206*	*24*	*394*	*370*
	22 2	18 9	3 2	55 7			**100.0**
	23 5	20 4	14 3	31 6			27 3
	6 0	5 2	0 9	15 2			27 3
50–69 years	*171*	*164*	*47*	*276*	*24*	*682*	*658*
	26 0	24 9	7 1	42 0			**100 0**
	49 0	47 8	56 0	49 9			48 5
	12 6	12.1	3 5	20 4			48 5
> 69 years	*89*	*102*	*24*	*76*	*6*	*297*	*291*
	30.6	35 1	8 2	26 2			**100.0**
	25 5	29 7	28 6	14 9			21 5
	6 6	7 5	1 8	5 6			21 5
Other	–	*1*	–	*1*	–	*2*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*349*	*343*	*84*	*580*	–	*1415*	*1356*
	25 7	25 3	6 2	42 8			**100 0**
	100.0	**100.0**	**100.0**	**100 0**			**100.0**
	25 7	25 3	6 2	42 8			**100.0**

TABLE f_c 20 *Age* versus *Nipple retraction.*

	Nipple retraction				
	Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
< 35 years	*6*	*30*	*6*	*42*	*36*
	16 7	83 3			**100.0**
	1 5	3 2			2 7
	0 5	2 3			2 7
35–49 years	*82*	*281*	*31*	*394*	*363*
	22 6	77 4			**100 0**
	20 6	30 2			27 3
	6 2	21 1			27 3
50–69 years	*209*	*435*	*38*	*682*	*644*
	32 5	67 5			**100 0**
	52 5	46 7			48 5
	15 7	32 7			48.5
> 69 years	*101*	*185*	*11*	*297*	*286*
	35 3	64 7			**100.0**
	25 4	19 9			21 5
	7 6	13 9			21 5
Other	–	*2*	–	*2*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*398*	*931*	–	*1415*	*1329*
	29 9	70 1			**100.0**
	100.0	**100.0**			**100.0**
	29 9	70 1			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 21 *Age* versus *Pectoral muscle fixation.*

Age	Pectoral muscle fixation: No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
< 35 years	*32*	*4*	*1*	*5*	*42*	*37*
	86.5	10.8	2.7			100.0
	3.0	2.4	1.1			2.8
	2.4	0.3	0.1			2.8
35–49 years	*301*	*39*	*22*	*32*	*394*	*362*
	83.1	10.8	6.1			100.0
	28.5	23.2	23.9			27.5
	22.9	3.0	1.7			27.5
50–69 years	*509*	*82*	*44*	*47*	*682*	*635*
	80.2	12.9	6.9			100.0
	48.2	48.8	47.8			48.3
	38.7	6.2	3.3			48.3
> 69 years	*214*	*43*	*25*	*15*	*297*	*282*
	75.9	15.2	8.9			100.0
	20.3	25.6	27.2			21.4
	16.3	3.3	1.9			21.4
Other	*2*	–	–	–	*2*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*1056*	*168*	*92*	–	*1415*	*1316*
	80.2	12.8	7.0			100.0
	100.0	100.0	100.0			100.0
	80.2	12.8	7.0			100.0

TABLE f_c 22 *Age* versus *Status of the homolateral axillary lymph nodes.*

Age	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
< 35 years	*9*	*6*	*2*	*23*	*2*	*42*	*40*
	22.5	15.0	5.0	57.5			100.0
	3.7	2.9	2.2	2.9			2.9
	0.7	0.4	0.1	1.7			2.9
35–49 years	*67*	*64*	*15*	*238*	*10*	*394*	*384*
	17.4	16.7	3.9	62.0			100.0
	27.7	30.8	16.3	28 6			27.9
	4.9	4.7	1.1	17.3			27.9
50–69 years	*108*	*95*	*51*	*409*	*19*	*682*	*663*
	16.3	14.3	7.7	61.7			100.0
	44.6	45.7	55.4	49.0			48.3
	7.9	6.9	3.7	29.8			48.3
> 69 years	*58*	*43*	*24*	*162*	*10*	*297*	*287*
	20.2	15.0	8.4	56.5			100.0
	24.0	20.7	26.1	19.5			20.9
	4.2	3.1	1.7	11.8			20.9
Other	–	–	*1*	*1*	–	*2*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*242*	*208*	*92*	*832*	–	*1415*	*1374*
	17.6	15.1	6.7	60.6			100.0
	100.0	100.0	100.0	100.0			100.0
	17.6	15.1	6.7	60.6			100.0

TABLE f_c 23 *Age* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Age	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
< 35 years	*4*	*38*	*42*	*4*
	100.0			100.0
	5.0			5.0
	5.0			5.0
35–49 years	*22*	*372*	*394*	*22*
	100.0			100.0
	27.5			27.5
	27.5			27.5
50–69 years	*37*	*645*	*682*	*37*
	100.0			100.0
	46.3			46.3
	46.3			46.3
> 69 years	*17*	*280*	*297*	*17*
	100.0			100.0
	21.3			21.3
	21.3			21.3
Other	–	*2*	*2*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*80*	–	*1415*	*80*
	100.0			100.0
	100.0			100.0
	100.0			100.0

TABLE f_c 24 *Age* versus *Clinical stage (International* TNM *classification).*

Age	Clinical stage (International TNM classification): Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
< 35 years	*14*	*5*	*22*	*1*	–	*42*	*42*
	33.3	11.9	52.4	2.4			100.0
	3.4	2.7	3.0	1.4			3.0
	1.0	0.4	1.6	0.1			3.0
35–49 years	*127*	*66*	*187*	*12*	*2*	*394*	*392*
	32.4	16.8	47.7	3.1			100.0
	30.8	36.1	25.2	17.4			27.8
	9.0	4.7	13.2	0.8			27.8
50–69 years	*196*	*88*	*350*	*42*	*6*	*682*	*676*
	29.0	13.0	51.8	6.2			100.0
	47.5	48.1	47.2	60.9			48.2
	14.0	6.2	24.9	3.0			48.2
> 69 years	*76*	*24*	*183*	*14*	–	*297*	*297*
	25.6	8.1	61.6	4.7			100.0
	18.4	13.1	24.7	20.3			21.0
	5.4	1.7	12.9	1.0			21.0
Other	*1*	–	*1*	–	–	*2*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*413*	*183*	*742*	*69*	–	*1415*	*1407*
	29.4	13.1	52.6	4.9			100.0
	100.0	100.0	100.0	100.0			100.0
	29.4	13.1	52.6	4.9			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 25 *Age* versus *Clinical stage (International* TNM *classification). Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms*

	Clinical stage (International TNM classification)							
Age	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
< 35 years	*14*	*5*	*12*	*10*	*1*	–	*42*	*42*
	33 3	11 9	28 6	23 8	2 4			**100 0**
	3 4	2 7	6 5	1 8	1 4			3 0
	1 0	0 4	0 9	0 7	0 1			3 0
35–49 years	*127*	*66*	*61*	*126*	*12*	*2*	*394*	*392*
	32 4	16 8	15 6	32 1	3 1			**100 0**
	30 8	36 1	33 2	22 6	17 4			27 9
	9 0	4 7	4 3	9 0	0 9			27 9
50–69 years	*196*	*88*	*85*	*265*	*42*	*6*	*682*	*676*
	29 0	13 0	12 6	39 2	6 2			**100 0**
	47 5	48 1	46 2	47 5	60 9			48 0
	13 9	6 3	6 0	18 8	3 0			48 0
> 69 years	*76*	*24*	*26*	*157*	*14*	–	*297*	*297*
	25 6	8 1	8 8	52 9	4 7			**100.0**
	18 4	13 1	14 1	28 1	20 3			21 1
	5 4	1 7	1 8	11 2	1 0			21 1
Other	*1*	–	–	*1*	–		*2*	–
Totals whole series	*414*	*183*	*184*	*559*	*69*	*8*	*1417*	*1409*
Totals noticed data	*413*	*183*	*184*	*558*	*69*	–	*1415*	*1407*
	29 4	13 0	13 1	39 7	4 9			**100 0**
	100 0	**100.0**	**100.0**	**100.0**	**100.0**			**100.0**
	29 4	13 0	13 1	39 7	4 9			**100 0**

TABLE fc 26 *Age* versus *Histology of the axillary lymph nodes.*

	Histology of the axillary lymph nodes				
Age	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
< 35 years	*8*	*24*	*10*	*42*	*32*
	25 0	75 0			**100.0**
	2 0	3 7			3 0
	0 8	2 3			3 0
35–49 years	*114*	*201*	*79*	*394*	*315*
	36 2	63 8			**100 0**
	28 4	30 9			29 9
	10 8	19 1			29 9
50–69 years	*209*	*327*	*146*	*682*	*536*
	39 0	61 0			**100.0**
	52 0	50 2			50 9
	19 8	31 1			50 9
> 69 years	*71*	*99*	*127*	*297*	*170*
	41 8	58 2			**100.0**
	17 7	15 2			16 1
	6 7	9 4			16 1
Other	–	*1*	*1*	*2*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*402*	*651*	–	*1415*	*1053*
	38 2	61 8			**100.0**
	100 0	**100.0**			**100.0**
	38 2	61 8			**100.0**

TABLE fc 27 *Duration of symptoms before starting treatment* versus *Age at onset of menopause.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Duration of symptoms before starting treatment	Age at onset of menopause						
	< 45 years	45-55 years	> 55 years	No menopause	Other	Totals whole series	Totals noticed data
0–30 days	*36*	*190*	*14*	*80*	*132*	*452*	*320*
	11.3	59.4	4.4	25.0			**100.0**
	32.4	37.4	40.0	36.4			36.6
	4.1	21.7	1.6	9.2			36.6
1–6 months	*33*	*157*	*11*	*73*	*166*	*440*	*274*
	12.0	57.3	4.0	26.6			**100.0**
	29.7	30.9	31.4	33.2			31.4
	3.8	18.0	1.3	8.4			31.4
> 6 months	*42*	*161*	*10*	*67*	*164*	*444*	*280*
	15.0	57.5	3.6	23.9			**100.0**
	37.8	31.7	28.6	30.5			32.0
	4.8	18.4	1.1	7.7			32.0
Other	*4*	*21*	*2*	*5*	*49*	*81*	–
Totals whole series	*115*	*529*	*37*	*225*	*511*	*1417*	*906*
Totals noticed data	*111*	*508*	*35*	*220*	–	*1336*	*874*
	12.7	58.1	4.0	25.2			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	12.7	58.1	4.0	25.2			**100.0**

TABLE fc 28 *Duration of symptoms before starting treatment* versus *Cause of menopause.*

Duration of symptoms before starting treatment	Cause of menopause					
	Spontaneous	Surgical or radiological castration	No menopause	Other	Totals whole series	Totals noticed data
0–30 days	*212*	*24*	*80*	*136*	*452*	*316*
	67.1	7.6	25.3			**100.0**
	36.1	36.4	36.4			36.2
	24.3	2.7	9.2			36.2
1–6 months	*178*	*25*	*74*	*163*	*440*	*277*
	64.3	9.0	26.7			**100.0**
	30.3	37.9	33.6			31.7
	20.4	2.9	8.5			31.7
> 6 months	*197*	*17*	*66*	*164*	*444*	*280*
	70.4	6.1	23.6			**100.0**
	33.6	25.8	30.0			32.1
	22.6	1.9	7.6			32.1
Other	*29*	*3*	*5*	*44*	*81*	–
Totals whole series	*616*	*69*	*225*	*507*	*1417*	*910*
Totals noticed data	*587*	*66*	*220*	–	*1336*	*873*
	67.2	7.6	25.2			**100.0**
	100.0	**100.0**	**100.0**			**100.0**
	67.2	7.6	25.2			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 29 *Duration of symptoms before starting treatment* versus *Location of tumor.*

Duration of symptoms before starting treatment	Location of tumor: Medial, subareolar, or whole breast	Lateral	Other	Totals whole series	Totals noticed data
0–30 days	*213*	*220*	*19*	*452*	*433*
	49 2	50 8			100.0
	30 4	39 1			34 3
	16 9	17 4			34 3
1–6 months	*224*	*190*	*26*	*440*	*414*
	54 1	45 9			100.0
	32 0	33 7			32 7
	17 7	15 0			32 7
> 6 months	*264*	*153*	*27*	*444*	*417*
	63 3	36 7			100.0
	37 7	27 2			33 0
	20 9	12 1			33 0
Other	*33*	*38*	*10*	*81*	–
Totals whole series	*734*	*601*	*82*	*1417*	*1335*
Totals noticed data	*701*	*563*	–	*1336*	*1264*
	55 5	44 5			100.0
	100.0	100.0			100.0
	55 5	44 5			100.0

TABLE fc 30 *Duration of symptoms before starting treatment* versus *Size of tumor.*

Duration of symptoms before starting treatment	Size of tumor: Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
0–30 days	*71*	*235*	*119*	*11*	*16*	*452*	*436*
	16 3	53 9	27 3	2 5			100.0
	38 4	41 9	28 3	11 8			34 6
	5 6	18 7	9 5	0 9			34 6
1–6 months	*65*	*187*	*132*	*27*	*29*	*440*	*411*
	15 8	45 5	32 1	6 6			100.0
	35 1	33 3	31 4	29 0			32 7
	5 2	14 9	10 6	2 1			32 7
> 6 months	*49*	*139*	*169*	*55*	*92*	*444*	*412*
	11 9	33 7	41 0	13 3			100.0
	26 5	24 8	40 2	59 1			32 7
	3 9	11 0	13 4	4 4			32 7
Other	*15*	*30*	*25*	*7*	*4*	*81*	–
Totals whole series	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
Totals noticed data	*185*	*561*	*420*	*93*	–	*1336*	*1259*
	14 7	44 6	33 4	7 4			100 0
	100.0	100.0	100.0	100 0			100.0
	14 7	44 6	33 4	7 4			100.0

TABLE f_c 31 *Duration of symptoms before starting treatment* versus *Fixation to skin.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Duration of symptoms before starting treatment	Fixation to skin: Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
0–30 days	*124*	*61*	*13*	*237*	*17*	*452*	*435*
	28 5	14 0	3 0	54 4			**100 0**
	37 5	19 1	16 0	44 2			34 0
	9 7	4 8	1 0	18 5			34 0
1–6 months	*119*	*98*	*22*	*178*	*23*	*440*	*417*
	28 5	23 5	5 3	42 6			**100 0**
	36 0	30 6	27 2	31 1			32 5
	9 3	7 6	1 7	13 9			32 5
> 6 months	*88*	*161*	*46*	*135*	*14*	*444*	*430*
	20 5	37 4	10 7	31 4			**100 0**
	26 6	50 3	56 8	24 7			33 5
	6 9	12 6	3 6	10 4			33 5
Other	*18*	*24*	*3*	*31*	*5*	*81*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*331*	*320*	*81*	*550*	–	*1336*	*1282*
	25 8	25 0	6 3	42 9			**100 0**
	100.0	**100 0**	**100 0**	**100 0**			**100.0**
	25 8	25 0	6 3	42 9			**100 0**

TABLE f_c 32 *Duration of symptoms before starting treatment* versus *Nipple retraction.*

Duration of symptoms before starting treatment	Nipple retraction: Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
0–30 days	*85*	*341*	*26*	*452*	*426*
	20 0	80 0			**100 0**
	22 5	38 7			33 8
	6 8	27 1			33 8
1–6 months	*118*	*292*	*30*	*440*	*410*
	28 8	71 2			**100 0**
	31 3	33 1			32 6
	9 4	23 2			32 6
> 6 months	*174*	*249*	*21*	*444*	*423*
	41 1	58 9			**100 0**
	46 2	28 2			33 6
	13 8	19 8			33 6
Other	*21*	*51*	*9*	*81*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*377*	*882*	–	*1336*	*1259*
	29 9	70 1			**100.0**
	100.0	**100 0**			**100.0**
	29 9	70 1			**100.0**

Numbers
% Horizonta
% Vertical
% Totals noticed data

TABLE f_c 33 *Duration of symptoms before starting treatment* versus *Pectoral muscle fixation.*

Duration of symptoms before starting treatment	Pectoral muscle fixation					
	No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
0–30 days	*368*	*46*	*8*	*30*	*452*	*422*
	87 2	10 9	1 9			**100 0**
	36 4	29 7	9 8			33 8
	29 5	3 7	0 6			33 8
1–6 months	*325*	*53*	*27*	*35*	*440*	*405*
	80 2	13 1	6 7			**100 0**
	32 2	34 2	32 9			32 5
	26 1	4 3	2 2			32 5
> 6 months	*317*	*56*	*47*	*24*	*444*	*420*
	75 5	13 3	11 2			**100.0**
	31 4	36 1	57 3			33 7
	25 4	4 5	3 8			33 7
Other	*48*	*13*	*10*	*10*	*81*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*1010*	*155*	*82*	–	*1336*	*1247*
	81 0	12 4	6 6			**100.0**
	100 0	**100 0**	**100.0**			**100 0**
	81 0	12 4	6 6			**100.0**

TABLE f_c 34 *Duration of symptoms before starting treatment* versus *Status of the homolateral axillary lymph nodes.*

Duration of symptoms before starting treatment	Status of the homolateral axillary lymph nodes						
	Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
0–30 days	*73*	*54*	*28*	*290*	*7*	*452*	*445*
	16 4	12 1	6 3	65 2			**100 0**
	32 2	28 0	30 8	36 6			34 2
	5 6	4 1	2 1	22 3			34 2
1–6 months	*81*	*62*	*22*	*260*	*15*	*440*	*425*
	19 1	14 6	5 2	61 0			**100 0**
	35 7	32 1	24 2	32 8			32 6
	6 2	4 8	1 7	20 0			32 6
> 6 months	*73*	*77*	*41*	*242*	*11*	*444*	*433*
	16 9	17 8	9 5	55 8			**100.0**
	32 2	39 9	45 1	30 6			33 2
	5 6	6 0	3 1	18 5			33 2
Other	*15*	*15*	*2*	*41*	*8*	*81*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*227*	*193*	*91*	*792*	–	*1336*	*1303*
	17 4	14 8	7 0	60 8			**100 0**
	100 0	**100 0**	**100 0**	**100.0**			**100 0**
	17 4	14 8	7 0	60 8			**100.0**

TABLE f_c 35 *Duration of symptoms before starting treatment* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Duration of symptoms before starting treatment	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
0–30 days	*15*	*437*	*452*	*15*
	100.0			**100.0**
	19.7			19.7
	19.7			19.7
1–6 months	*26*	*414*	*440*	*26*
	100.0			**100.0**
	34.2			34.2
	34.2			34.2
> 6 months	*35*	*409*	*444*	*35*
	100.0			**100.0**
	46.1			46.1
	46.1			46.1
Other	*4*	*77*	*81*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*76*	–	*1336*	*76*
	100.0			**100.0**
	100.0			**100.0**
	100.0			**100.0**

TABLE f_c 36 *Duration of symptoms before starting treatment* versus *Clinical stage (International* TNM *classification).*

Duration of symptoms before starting treatment	Clinical stage (International TNM classification): Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
0–30 days	*172*	*70*	*197*	*11*	*2*	*452*	*450*
	38.2	15.6	43.8	2.4			**100.0**
	43.8	40 2	28.1	17.5			33.8
	12.9	5.2	14.9	0.8			33.8
1–6 months	*131*	*64*	*232*	*13*	–	*440*	*440*
	29.8	14.5	52.7	3.0			**100.0**
	33.3	36.8	33.1	20.6			33.0
	9.8	4.8	17.4	1.0			33.0
> 6 months	*90*	*40*	*272*	*39*	*3*	*444*	*441*
	20.4	9.1	61.7	8.8			**100.0**
	22.9	23.0	38.8	61.9			33.2
	6.7	3.0	20.4	3.1			33.2
Other	*21*	*9*	*42*	*6*	*3*	*81*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*393*	*174*	*701*	*63*	–	*1336*	*1331*
	29.4	13.0	52.7	4.9			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	29.4	13.0	52.7	4.9			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 37 *Duration of symptoms before starting treatment* versus *Clinical stage (International* TNM *classification). Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms.*

	Clinical stage (International TNM classification)							
Duration of symptoms before starting treatment	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
0–30 days	*172*	*70*	*67*	*130*	*11*	*2*	*452*	*450*
	38 2	15 6	14 9	28 9	2 4			**100.0**
	43 8	40 2	37 9	24 8	17 5			33 8
	12 9	5 3	5 0	9 8	0 8			33 8
1–6 months	*131*	*64*	*60*	*172*	*13*	–	*440*	*440*
	29 8	14 5	13 6	39 1	3 0			**100.0**
	33 3	36 8	33 9	32 8	20 6			33 0
	9 8	4 8	4 5	12 9	1 0			33 0
> 6 months	*90*	*40*	*50*	*222*	*39*	*3*	*444*	*441*
	20 4	9 1	11 3	50 3	8 8			**100.0**
	22 9	23 0	28 2	42 4	61 9			33 2
	6 8	3 0	3 8	16 7	2 9			33 2
Other	*21*	*9*	*7*	*35*	*6*	*3*	*81*	–
Totals whole series	*414*	*183*	*184*	*559*	*69*	*8*	*1417*	*1409*
Totals noticed data	*393*	*174*	*177*	*524*	*63*	–	*1336*	*1331*
	29 5	13 1	13 3	39 4	4 7			**100.0**
	100.0	**100.0**	**100.0**	**100.0**	**100.0**			**100 0**
	29 5	13 1	13 3	39 4	4 7			**100.0**

TABLE f_c 38 *Duration of symptoms before starting treatment* versus *Histology of the axillary lymph nodes.*

	Histology of the axillary lymph nodes				
Duration of symptoms before starting treatment	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
0–30 days	*164*	*198*	*90*	*452*	*362*
	45 3	54 7			**100.0**
	42 9	32 0			36 2
	16 4	19 8			36 2
1–6 months	*119*	*218*	*103*	*440*	*337*
	35 3	64 7			**100.0**
	31 2	35 2			33 7
	11 9	21 8			33 7
> 6 months	*99*	*203*	*142*	*444*	*302*
	32.8	67 2			**100 0**
	25.9	32 8			30 2
	9 9	20 3			30 2
Other	*20*	*33*	*28*	*81*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*382*	*619*	–	*1336*	*1001*
	38.2	61 8			**100.0**
	100.0	**100.0**			**100.0**
	38 2	61 8			**100.0**

TABLE fc 39 *Age at onset of menopause* versus *Cause of menopause.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Age at onset of menopause	Cause of menopause: Spontaneous	Surgical or radiological castration	No menopause	Other	Totals whole series	Totals noticed data
< 45 years	*80*	*28*	–	*7*	*115*	*108*
	74.1	25.9				**100.0**
	13.6	44.4				12.3
	9.1	3.2				12.3
45–55 years	*474*	*34*	–	*21*	*529*	*508*
	93.3	6.7				**100.0**
	80.5	54.0				57.9
	54.0	3.9				57.9
> 55 years	*35*	*1*	–	*1*	*37*	*36*
	97.2	2.8				**100.0**
	5.9	1.6				4.1
	4.0	0.1				4.1
No menopause	–	–	*225*	–	*225*	*225*
			100.0			**100.0**
			100.0			25.7
			25.7			25.7
Other	*27*	*6*	–	*478*	*511*	–
Totals whole series	*616*	*69*	*225*	*507*	*1417*	*910*
Totals noticed data	*589*	*63*	*225*	–	*906*	*877*
	67.2	7.2	25.7			**100.0**
	100.0	**100.0**	**100.0**			**100.0**
	67.2	7.2	25.7			**100.0**

TABLE fc 40 *Age at onset of menopause* versus *Location of tumor.*

Age at onset of menopause	Location of tumor: Medial, subareolar or whole breast	Lateral	Other	Totals whole series	Totals noticed data
< 45 years	*65*	*44*	*6*	*115*	*109*
	59.6	40.4			**100.0**
	13.0	12.4			12.7
	7.6	5.1			12.7
45–55 years	*290*	*213*	*26*	*529*	*503*
	57.7	42.3			**100.0**
	58.1	59.8			58.8
	33.9	24.9			58.8
> 55 years	*21*	*14*	*2*	*37*	*35*
	60.0	40.0			**100.0**
	4.2	3.9			4.1
	2.5	1.6			4.1
No menopause	*123*	*85*	*17*	*225*	*208*
	59.1	40.9			**100.0**
	24.6	23.9			24.3
	14.4	9.9			24.3
Other	*235*	*245*	*31*	*511*	–
Totals whole series	*734*	*601*	*82*	*1417*	*1335*
Totals noticed data	*499*	*356*	–	*906*	*855*
	58.4	41.6			**100.0**
	100.0	**100.0**			**100.0**
	58.4	41.6			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 41 *Age at onset of menopause* versus *Size of tumor.*

Age at onset of menopause	Size of tumor: Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
< 45 years	*13*	*58*	*31*	*3*	*10*	*115*	*105*
	12 4	55 2	29 5	2 9			100 0
	9 7	13 9	12 1	5 8			12 5
	1 6	6 8	3 7	0 4			12 5
45–55 years	*74*	*239*	*154*	*35*	*27*	*529*	*502*
	14 7	47 6	30 7	7 0			100 0
	55 2	57 2	60 2	67 3			58 3
	8 7	27 7	17 8	4 1			58 3
> 55 years	*4*	*23*	*8*	*2*	–	*37*	*37*
	10 8	62 2	21 6	5 4			100.0
	3 0	5 5	3 1	3 8			4 3
	0 5	2 7	0 9	0 2			4 3
No menopause	*43*	*98*	*63*	*12*	*9*	*225*	*216*
	19 9	45 4	29 2	5 6			100 0
	32 1	23 4	24 6	23 1			25 0
	5 0	11 3	7 3	1 4			25 0
Other	*66*	*173*	*189*	*48*	*35*	*511*	–
Totals whole series	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
Totals noticed data	*134*	*418*	*256*	*52*	–	*906*	*860*
	15 7	48 5	29 7	6 1			100.0
	100.0	100.0	100 0	100.0			100.0
	15 7	48 5	29 7	6 1			100.0

TABLE f_c 42 *Age at onset of menopause* versus *Fixation to skin.*

Age at onset of menopause	Fixation to skin: Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
< 45 years	*39*	*26*	*4*	*41*	*5*	*115*	*110*
	35 5	23 6	3 6	37 3			100.0
	15 4	13 5	7 8	10 6			12 5
	4 4	2 9	0 5	4 8			12 5
45–55 years	*164*	*121*	*35*	*202*	*7*	*529*	*522*
	31 4	23 2	6 7	38 7			100 0
	65 1	63 0	68 6	52 1			59 1
	18 6	13 7	4 0	22 8			59 1
> 55 years	*11*	*9*	*2*	*13*	*2*	*37*	*35*
	31 4	25 7	5 7	37 2			100.0
	4 4	4 7	3 9	3 3			4 0
	1 2	1 0	0 2	1 5			4 0
No menopause	*38*	*36*	*10*	*132*	*9*	*225*	*216*
	17 6	16 7	4 6	61 1			100.0
	15 1	18 8	19 6	34 0			24 5
	4 3	4 1	1 1	14 9			24 5
Other	*97*	*152*	*33*	*193*	*36*	*511*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*252*	*192*	*51*	*388*	–	*906*	*883*
	28 5	21 7	5 8	44 0			100.0
	100 0	100 0	100.0	100.0			100.0
	28 5	21 7	5 8	44 0			100.0

TABLE fc 43 *Age at onset of menopause* versus *Nipple retraction*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Age at onset of menopause	Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
	Nipple retraction				
< 45 years	*30*	*81*	*4*	*115*	*111*
	27 0	73 0			**100.0**
	11 4	13 2			12 7
	3 4	9 3			12 7
45–55 years	*178*	*337*	*14*	*529*	*515*
	34 6	65 4			**100.0**
	67 7	55 1			58 9
	20 3	38 5			58 9
< 55 years	*12*	*23*	*2*	*37*	*35*
	34 3	65 7			**100 0**
	4 6	3 8			4 0
	1 4	2 6			4 0
No menopause	*43*	*171*	*11*	*225*	*214*
	20 1	79 9			**100.0**
	16 3	27 9			24 5
	4 9	19 5			24 5
Other	*135*	*321*	*55*	*511*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*263*	*612*	–	*906*	*875*
	30 1	69 9			**100.0**
	100 0	**100 0**			**100 0**
	30 1	69 9			**100.0**

TABLE fc 44 *Age at onset of menopause* versus *Pectoral muscle fixation.*

Age at onset of menopause	No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
	Pectoral muscle fixation					
< 45 years	*86*	*14*	*10*	*5*	*115*	*110*
	78 2	12 7	9 1			**100.0**
	12 4	11 7	17 9			12 7
	9 9	1 6	1 2			12 7
45–55 years	*407*	*76*	*30*	*16*	*529*	*513*
	79 3	14 8	5 8			**100 0**
	58 7	63 3	53 6			59 0
	46 8	8 7	3 5			59 0
> 55 years	*27*	*3*	*4*	*3*	*37*	*34*
	79 4	8 8	11 8			**100.0**
	3 9	2 5	7 1			3 9
	3 1	0 3	0 5			3 9
No menopause	*173*	*27*	*12*	*13*	*225*	*212*
	81 6	12 7	5 7			**100 0**
	25 0	22 5	21 4			24 4
	19 9	3 1	1 4			24 4
Other	*365*	*48*	*36*	*62*	*511*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*693*	*120*	*56*	–	*906*	*869*
	79 7	13 8	6 4			**100.0**
	100.0	**100.0**	**100.0**			**100 0**
	79.7	13 8	6 4			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 45 *Age at onset of menopause* versus *Status of the homolateral axillary lymph nodes.*

Age at onset of menopause	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
< 45 years	*21*	*9*	*10*	*71*	*4*	*115*	*111*
	18.9	8.1	9.0	64.0			**100.0**
	13.0	8.0	15.2	13.0			12.5
	2.4	1.0	1.1	7.9			12.5
45–55 years	*90*	*76*	*42*	*312*	*9*	*529*	*520*
	17.3	14.6	8.1	60.0			**100.0**
	55.6	67.3	63.6	56.8			58.5
	10.1	8.5	4.7	35.2			58.5
> 55 years	*8*	*3*	*5*	*21*	–	*37*	*37*
	21.6	8.1	13.5	56.8			**100.0**
	4.9	2.7	7.6	3.8			4.2
	0.9	0.3	0.6	2.4			4.2
No menopause	*43*	*25*	*9*	*144*	*4*	*225*	*221*
	19.5	11.3	4.1	65.2			**100.0**
	26.5	22.1	13.6	26.4			24.9
	4.8	2.8	1.0	16.3			24.9
Other	*80*	*95*	*27*	*285*	*24*	*511*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*162*	*113*	*66*	*548*	–	*906*	*889*
	18.2	12.7	7.4	61.8			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	18.2	12.7	7.4	61.8			**100.0**

TABLE fc 46 *Age at onset of menopause* versus *Status of the supra- and infraclavicular lymph nodes.*

Age at onset of menopause	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
< 45 years	*6*	*109*	*115*	*6*
	100.0			**100.0**
	11.5			11.5
	11.5			11.5
45–55 years	*33*	*496*	*529*	*33*
	100.0			**100.0**
	63.5			63.5
	63.5			63.5
> 55 years	*1*	*36*	*37*	*1*
	100.0			**100.0**
	1.9			1.9
	1.9			1.9
No menopause	*12*	*213*	*225*	*12*
	100.0			**100.0**
	23.1			23.1
	23.1			23.1
Other	*28*	*483*	*511*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*52*	–	*906*	*52*
	100.0			**100.0**
	100.0			**100.0**
	100,0			**100.0**

TABLE fc 47 *Age at onset of menopause* versus *Clinical stage (International* TNM *classification).*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Age at onset of menopause	Clinical stage (International TNM classification)						
	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
< 45 years	*34*	*15*	*57*	*5*	*4*	*115*	*111*
	30.6	13.5	51.4	4.5			100.0
	11.5	12.8	12.9	10.9			12.7
	3.9	1.7	6.4	0.7			12.7
45–55 years	*168*	*59*	*274*	*28*	–	*529*	*529*
	31.8	11.2	51.8	5.3			100.0
	56.9	50.4	61.9	60.9			58.4
	18.5	6.5	30.2	3.1			58.4
> 55 years	*13*	*6*	*16*	*2*	–	*37*	*37*
	35.1	16.2	43.2	5.4			100.0
	4.4	5.1	3.6	4.3			4.1
	1.4	0.7	1.8	0.2			4.1
No menopause	*80*	*37*	*96*	*11*	*1*	*225*	*224*
	35.7	16.5	42.8	5.0			100.0
	27.1	31.6	21.6	23.9			24.8
	8.9	4.1	10.6	1.2			24.8
Other	*119*	*66*	*300*	*23*	*3*	*511*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*295*	*117*	*443*	*46*	–	*906*	*901*
	32.7	13.0	49.0	5.2			100.0
	100.0	100.0	100.0	100.0			100.0
	32.7	13.0	49.0	5.2			100.0

TABLE fc 48 *Age at onset of menopause* versus *Histology of the axillary lymph nodes.*

Age at onset of menopause	Histology of the axillary lymph nodes				
	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
< 45 years	*38*	*46*	*31*	*115*	*84*
	45.2	54.8			100.0
	13.8	11.0			12.1
	5.5	6.6			12.1
45–55 years	*164*	*234*	*131*	*529*	*398*
	41.2	58.8			100.0
	59.6	55.8			57.3
	23.6	33.7			57.3
> 55 years	*10*	*21*	*6*	*37*	*31*
	32.3	67.7			100.0
	3.6	5.0			4.5
	1.4	3.0			4.5
No menopause	*63*	*118*	*44*	*225*	*181*
	34.8	65.2			100.0
	22.9	28.2			26.1
	9.1	17.0			26.1
Other	*127*	*233*	*151*	*511*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*275*	*419*	–	*906*	*694*
	39.6	60.4			100.0
	100.0	100.0			100.0
	39.6	60.4			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 49 *Cause of menopause* versus *Location of tumor.*

Cause of menopause	Location of tumor: Medial, subareolar, or whole breast	Lateral	Other	Totals whole series	Totals noticed data
Spontaneous	*344*	*244*	*28*	*616*	*588*
	58 5	41 5			**100.0**
	68 8	67 8			68 4
	40 0	28 4			68 4
Surgical or radiological castration	*33*	*30*	*6*	*69*	*63*
	52 4	47 6			**100.0**
	6 6	8 3			7 3
	3 8	3 5			7 3
No menopause	*123*	*86*	*16*	*225*	*209*
	58 9	41 1			**100.0**
	24 6	23 9			24 3
	14 3	10 0			24 3
Other	*234*	*241*	*32*	*507*	
Totals whole series	*734*	*601*	*82*	*1417*	*1335*
Totals noticed data	*500*	*360*	–	*910*	*860*
	58 1	41 9			**100 0**
	100.0	**100.0**			**100.0**
	58 1	41 9			**100.0**

TABLE f_c 50 *Cause of menopause* versus *Size of tumor.*

Cause of menopause	Size of tumor: Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
Spontaneous	*77*	*291*	*173*	*41*	*34*	*616*	*582*
	13 2	50 0	29 7	7 0			**100 0**
	57 5	69 1	68 1	74 5			67 4
	8 9	33 7	20 0	4 7			67 4
Surgical or radiological castration	*13*	*32*	*19*	*2*	*3*	*69*	*66*
	19 7	48 5	28 8	3 0			**100.0**
	9 7	7 6	7 5	3 6			7 6
	1 5	3 7	2 2	0 2			7 6
No menopause	*44*	*98*	*62*	*12*	*9*	*225*	*216*
	20 4	45 4	28 7	5 6			**100.0**
	32 8	23 3	24 4	21 8			25 0
	5 1	11 3	7 2	1 4			25 0
Other	*66*	*170*	*191*	*45*	*35*	*507*	–
Totals whole series	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
Totals noticed data	*134*	*421*	*254*	*55*	–	*910*	*864*
	15 5	48 7	29 4	6 4			**100 0**
	100.0	**100.0**	**100.0**	**100.0**			**100 0**
	15 5	48 7	29 4	6 4			**100.0**

TABLE f_c 51 *Cause of menopause* versus *Fixation to skin*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Fixation to skin						
Cause of menopause	Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
Spontaneous	*188*	*150*	*41*	*229*	*8*	*616*	*608*
	30 9	24 7	6 7	37 7			**100 0**
	77 4	75 8	78 8	58 0			68 5
	21 2	16 9	4 6	25 8			68 5
Surgical or radiological castration	*17*	*12*	*1*	*34*	*5*	*69*	*64*
	26 6	18 8	1 6	53 0			**100 0**
	7 0	6 1	1 9	9 0			7 2
	1 9	1 4	0 1	3 8			7 2
No menopause	*38*	*36*	*10*	*132*	*9*	*225*	*216*
	17 6	16 7	4 6	61 1			**100 0**
	15 6	18 2	19 2	32 9			24 3
	4 3	4 1	1 1	14 8			24 3
Other	*106*	*146*	*32*	*186*	*37*	*507*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*243*	*198*	*52*	*395*	–	*910*	*888*
	27 4	22 3	5 9	44 4			**100 0**
	100 0	**100 0**	**100 0**	**100 0**			**100 0**
	27 4	22 3	5 9	44 4			**100 0**

TABLE f_c 52 *Cause of menopause* versus *Nipple retraction.*

	Nipple retraction				
Cause of menopause	Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
Spontaneous	*202*	*402*	*12*	*616*	*604*
	33 4	66 6			**100 0**
	77 7	64 4			68 3
	22 9	45 5			68 3
Surgical or radiological castration	*15*	*51*	*3*	*69*	*66*
	22 7	77 3			**100 0**
	5 8	8 2			7 5
	1 7	5 8			7 5
No menopause	*43*	*171*	*11*	*225*	*214*
	20 1	79 9			**100 0**
	16 5	27 4			24 2
	4 9	19 3			24 2
Other	*138*	*309*	*60*	*507*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*260*	*624*	–	*910*	*884*
	29 4	70 6			**100 0**
	100 0	**100 0**			**100 0**
	29 4	70 6			**100 0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 53 *Cause of menopause* versus *Pectoral muscle fixation.*

Cause of menopause	Pectoral muscle fixation: No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
Spontaneous	*471*	*82*	*46*	*17*	*616*	*599*
	78 6	13 7	7 7			100.0
	67 6	68 3	76 7			68 3
	53 7	9 4	5 2			68 3
Surgical or radiological castration	*53*	*11*	*2*	*3*	*69*	*66*
	80 3	16 7	3 0			100.0
	7 6	9 2	3 3			7 5
	6 0	1 3	0 2			7 5
No menopause	*173*	*27*	*12*	*13*	*225*	*212*
	81 6	12 7	5 7			100.0
	24 8	22 5	20 0			24 2
	19 7	3 1	1 4			24 2
Other	*361*	*48*	*32*	*66*	*507*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*697*	*120*	*60*	–	*910*	*877*
	79 5	13 7	6 8			100.0
	100.0	100.0	100.0			100 0
	79 5	13 7	6 8			100.0

TABLE f_c 54 *Cause of menopause* versus *Status of the homolateral axillary lymph nodes.*

Cause of menopause	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
Spontaneous	*110*	*79*	*52*	*363*	*12*	*616*	*604*
	18 2	13 1	8 6	60 1			100.0
	67 9	68 7	78 8	66 2			67 8
	12 3	8 9	5 8	40 8			67 8
Surgical or radiological castration	*9*	*11*	*5*	*41*	*3*	*69*	*66*
	13 6	16 7	7 6	62 1			100.0
	5 6	9 6	7 6	7 5			7 4
	1 0	1 2	0 6	4 6			7 4
No menopause	*43*	*25*	*9*	*144*	*4*	*225*	*221*
	19 5	11 3	4 1	65.1			100.0
	26 5	21 7	13 6	26 3			24 8
	4 8	2 8	1 0	16 2			24 8
Other	*80*	*93*	*27*	*285*	*22*	*507*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*162*	*115*	*66*	*548*	–	*910*	*891*
	18 1	12 9	7 4	61 6			100.0
	100.0	100.0	100.0	100.0			100.0
	18 1	12 9	7 4	61 6			100.0

TABLE f_c 55 *Cause of menopause* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Status of the supra and infraclavicular lymph nodes			
Cause of menopause	Considered to contain growth	Other	Totals whole series	Totals noticed data
Spontaneous	*41*	*575*	*616*	*41*
	100 0			**100 0**
	73 2			73 2
	73 2			73 2
Surgical or radiological castration	*3*	*66*	*69*	*3*
	100 0			**100 0**
	5 4			5 4
	5 4			5 4
No menopause	*12*	*213*	*225*	*12*
	100 0			**100 0**
	21 4			21 4
	21 4			21 4
Other	*24*	*483*	*507*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*56*	–	*910*	*56*
	100 0			**100 0**
	100 0			**100 0**
	100 0			**100 0**

TABLE f_c 56 *Cause of menopause* versus *Clinical stage (International* TNM *classification).*

	Clinical stage (International TNM classification)						
Cause of menopause	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Spontaneous	*190*	*73*	*321*	*29*	*3*	*616*	*613*
	31 0	12 1	52 2	4 7			**100 0**
	64 6	61 9	71 5	64 4			67 7
	21 0	8 2	35 3	3 2			67 7
Surgical or radiological castration	*23*	*9*	*32*	*5*	–	*69*	*69*
	33 3	13 0	46 4	7 2			**100 0**
	7 8	7 6	7 1	11 1			7 6
	2 5	1 0	3 5	0 5			7 6
No menopause	*81*	*36*	*96*	*11*	*1*	*225*	*224*
	36 1	16 1	42 8	5 0			**100 0**
	27 6	30 5	21 4	24 4			24 7
	9 0	4 0	10 5	1 2			24 7
Other	*120*	*65*	*294*	*24*	*4*	*507*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*294*	*118*	*449*	*45*	–	*910*	*906*
	32 5	13 2	49 3	4 9			**100 0**
	100 0	**100 0**	**100 0**	**100 0**			**100 0**
	32 5	13 2	49 3	4 9			**100 0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 57 *Cause of menopause* versus *Histology of the axillary lymph nodes.*

	Histology of the axillary lymph nodes				
Cause of menopause	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Spontaneous	*191*	*273*	*152*	*616*	*464*
	41 2	58 8			**100.0**
	68 2	65 2			66 4
	27 3	39 1			66 4
Surgical or radiological castration	*25*	*29*	*15*	*69*	*54*
	46 3	53 7			**100.0**
	8 9	6 9			7 7
	3 6	4 1			7 7
No menopause	*64*	*117*	*44*	*225*	*181*
	35 4	64 6			**100.0**
	22 9	27 9			25 9
	9 2	16 7			25 9
Other	*122*	*233*	*152*	*507*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*280*	*419*	–	*910*	*699*
	40 1	59 9			**100.0**
	100.0	**100 0**			**100.0**
	40 1	59 9			100 0

TABLE f_c 58 *Location of tumor* versus *Size of tumor.*

	Size of tumor						
Location of tumor	Not more than 2 cm	2–5 cm	5–10 cm	More than 10 cm	Other	Totals whole series	Totals noticed data
Medial, subareolar or whole breast	*91*	*303*	*222*	*80*	*38*	*734*	*696*
	13 1	43 5	31 9	11 5			**100.0**
	50 6	53 3	52 7	80 0			54 8
	7 2	23 9	17 5	6 3			54 8
Lateral	*89*	*266*	*199*	*20*	*27*	*601*	*574*
	15 5	46 3	34 7	3 5			**100.0**
	49 4	46 7	47 3	20 0			45 2
	7 0	20 9	15 7	1 6			45 2
Other	*20*	*22*	*24*	–	*16*	*82*	–
Totals whole series	*200*	*591*	*445*	*100*	*81*	*1417*	*1336*
Totals noticed data	*180*	*569*	*421*	*100*	–	*1335*	*1270*
	14 2	44 8	33 1	7 9			**100.0**
	100.0	**100 0**	**100 0**	**100 0**			**100.0**
	14 2	44 8	33 1	7 9			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 59 *Location of tumor* versus *Fixation to skin.*

	Fixation to skin						
Location of tumor	Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
Medial, subareolar or whole breast	*169*	*200*	*66*	*282*	*17*	*734*	*717*
	23 6	27 9	9 2	39 3			**100.0**
	50 1	59 3	79 5	55 5			55 4
	13 1	15 4	5 1	21 8			55 4
Lateral	*168*	*137*	*17*	*256*	*23*	*601*	*578*
	29 1	23 7	2 9	44 2			**100.0**
	49 9	40 7	20 5	44 5			44 6
	13 0	10 6	1 3	19 7			44 6
Other	*12*	*7*	*1*	*43*	*19*	*82*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*337*	*337*	*83*	*538*	–	*1335*	*1295*
	26 0	26 0	6 4	41 5			**100 0**
	100.0	**100.0**	**100 0**	**100.0**			**100.0**
	26 0	26 0	6 4	41 5			**100 0**

TABLE f_c 60 *Location of tumor* versus *Nipple retraction.*

	Nipple retraction				
Location of tumor	Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
Medial, subareolar or whole breast	*276*	*430*	*28*	*734*	*706*
	39 1	60 9			**100.0**
	72 1	48 5			55 6
	21 7	33 9			55 6
Lateral	*107*	*456*	*38*	*601*	*563*
	19 0	81 0			**100.0**
	27 9	51 5			44 4
	8 4	35 9			44 4
Other	*15*	*47*	*20*	*82*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*383*	*886*	–	*1335*	*1269*
	30 2	69 8			**100.0**
	100.0	**100.0**			**100 0**
	30 2	69 8			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 61 *Location of tumor* versus *Pectoral muscle fixation.*

Location of tumor	Pectoral muscle fixation: No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Total noticed data
Medial, subareolar or whole breast	*540*	*100*	*61*	*33*	*734*	*701*
	77 0	14 3	8 7			**100.0**
	53 8	61 7	67 0			55 8
	43 0	8 0	4 9			55 8
Lateral	*463*	*62*	*30*	*46*	*601*	*555*
	83 4	11 2	5 4			**100.0**
	46 2	38 3	33 0			44 2
	36 9	4 9	2 4			44 2
Other	*55*	*6*	*1*	*20*	*82*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*1003*	*162*	*91*	–	*1335*	*1256*
	79 9	12 9	7 2			**100 0**
	100.0	**100.0**	**100.0**			**100.0**
	79 9	12 9	7 2			**100.0**

TABLE f_c 62 *Location of tumor* versus *Status of the homolateral axillary lymph nodes.*

Location of tumor	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
Medial, subareolar or whole breast	*118*	*102*	*54*	*444*	*16*	*734*	*718*
	16 4	14 2	7 5	61 8			**100.0**
	52 4	51 8	59 3	56 2			55 1
	9 1	7 8	4 1	34 0			55 1
Lateral	*107*	*95*	*37*	*346*	*16*	*601*	*585*
	18 3	16 2	6 3	59 1			**100.0**
	47 6	48 2	40 7	43 8			44 9
	8 2	7 3	2 8	26 6			44 9
Other	*17*	*11*	*2*	*43*	*9*	*82*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*225*	*197*	*91*	*790*	–	*1335*	*1303*
	17 3	15 1	7 0	60 6			**100.0**
	100 0	**100.0**	**100.0**	**100 0**			**100 0**
	17 3	15 1	7 0	60 6			**100.0**

TABLE f_c 63 *Location of tumor* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Location of tumor	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
Medial, subareolar or whole breast	*49*	*685*	*734*	*49*
	100 0			**100.0**
	63 6			63 6
	63 6			63 6
Lateral	*28*	*573*	*601*	*28*
	100 0			**100.0**
	36 4			36 4
	36 4			36 4
Other	*3*	*79*	*82*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*77*	–	*1335*	*77*
	100 0			**100.0**
	100.0			**100.0**
	100 0			**100.0**

TABLE f_c 64 *Location of tumor* versus *Clinical stage (International* TNM *classification).*

Location of tumor	Clinical stage (International TNM classification): Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Medial, subareolar or whole breast	*205*	*74*	*403*	*51*	*1*	*734*	*733*
	28 1	9 8	55 0	7 1			**100.0**
	53 9	44 3	56 0	79 7			55 0
	15 4	5 5	30 2	3 8			55 0
Lateral	*175*	*93*	*317*	*13*	*3*	*601*	*598*
	29 3	15 6	53 0	2 2			**100.0**
	46 1	55 7	44 0	20 3			45 0
	13 1	7 0	23 9	1 0			45 0
Other	*34*	*16*	*23*	*5*	*4*	*82*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*380*	*167*	*720*	*64*	–	*1335*	*1331*
	28 6	12 6	53 9	4 9			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	28 6	12 6	53 9	4 9			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 65 *Location of tumor* versus *Clinical stage (International* TNM *classification) Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms.*

	Clinical stage (International TNM classification)							
Location of tumor	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
Medial,	*205*	*74*	*81*	*322*	*51*	*1*	*734*	*733*
subareolar or	28 0	10 1	11 1	43 9	7 0			**100 0**
whole breast	53 9	44 3	46 3	59 1	79 7			55 1
	15 4	5 6	6 1	24 2	3 8			55 1
Lateral	*175*	*93*	*94*	*223*	*13*	*3*	*601*	*598*
	29 3	15 6	15 7	37 3	2 2			**100 0**
	46 1	55 7	53 7	40 9	20 3			44 9
	13 1	7 0	7 1	16 8	1 0			44 9
Other	*34*	*16*	*9*	*14*	*5*	*4*	*82*	–
Totals whole series	*414*	*183*	*184*	*559*	*69*	*8*	*1417*	*1409*
Totals noticed data	*380*	*167*	*175*	*545*	*64*	–	*1335*	*1331*
	28 5	12 6	13 2	40 9	4 8			**100 0**
	100 0	**100 0**	**100 0**	**100 0**	**100 0**			**100 0**
	28 5	12 6	13 2	40 9	4 8			**100 0**

TABLE fc 66 *Location of tumor* versus *Histology of the axillary lymph nodes.*

	Histology of the axillary lymph nodes				
Location of tumor	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Medial, subareolar or	*194*	*326*	*214*	*734*	*520*
whole breast	37 3	62 7			**100 0**
	51 1	52 9			52 2
	19 5	32 7			52 2
Lateral	*186*	*290*	*125*	*601*	*476*
	39 1	60 9			**100 0**
	48 9	47 1			47 8
	18 7	29 1			47 8
Other	*22*	*36*	*24*	*82*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*380*	*616*	–	*1335*	*996*
	38 2	61 8			**100 0**
	100 0	**100 0**			**100 0**
	38 2	61 8			**100.0**

TABLE f_c 67 *Size of tumor* versus *Fixation to skin.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Fixation to skin						
Size of tumor	Incomplete skin fixation	Complete skin fixation	Skin fixation wide of tumor but not beyond breast area	Skin not involved	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*32*	*18*	*1*	*136*	*13*	*200*	*187*
	17 1	9 6	0 5	72 8			100.0
	9 7	5 5	1 3	24 7			15 0
	2 5	1 4	0 1	11 0			15 0
2–5 cm	*180*	*115*	*8*	*265*	*23*	*591*	*568*
	31 7	20 2	1 4	46 7			100.0
	54 5	35 3	10 1	48 1			44 3
	13 9	8 9	0 6	20 9			44 3
5–10 cm	*109*	*155*	*34*	*135*	*12*	*445*	*433*
	25 2	35 8	7 9	31 1			100 0
	33 0	47 5	43 0	24 5			33 2
	8 4	12 0	2 6	10 2			33 2
More than 10 cm	*9*	*38*	*36*	*15*	*2*	*100*	*98*
	9 2	38 8	36 7	15 3			100.0
	2 7	11 7	45 6	2 7			7 5
	0 7	2 9	2 8	1 1			7 5
Other	*19*	*18*	*5*	*30*	*9*	*81*	–
Totals whole series	*349*	*344*	*84*	*581*	*59*	*1417*	*1358*
Totals noticed data	*330*	*326*	*79*	*551*	–	*1336*	*1286*
	25 5	25 3	6 1	43 1			100 0
	100 0	100.0	100.0	100.0			100.0
	25 5	25 3	6 1	43 1			100 0

TABLE f_c 68 *Size of tumor* versus *Nipple retraction.*

	Nipple retraction				
Size of tumor	Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*23*	*162*	*15*	*200*	*185*
	12 4	87 6			100.0
	6 2	18 2			14 7
	1 8	12 8			14 7
2–5 cm	*127*	*434*	*30*	*591*	*561*
	22 6	77 4			100.0
	34 1	48 8			44 5
	10 1	34 4			44 5
5–10 cm	*171*	*248*	*26*	*445*	*419*
	40 8	59 2			100.0
	46 0	27 9			33 2
	13 6	19 7			33 2
More than 10 cm	*51*	*45*	*4*	*100*	*96*
	53 1	46 9			100.0
	13 7	5 1			7 6
	4 0	3 6			7 6
Other	*26*	*44*	*11*	*81*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*372*	*889*	–	*1336*	*1261*
	29 5	70 5			100.0
	100 0	100 0			100 0
	29 5	70 5			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 69 *Size of tumor* versus *Pectoral muscle fixation.*

Size of tumor	Pectoral muscle fixation: No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*178*	*5*	*2*	*15*	*200*	*185*
	96.2	2.7	1.1			100.0
	17.9	3.0	2.2			14.8
	14.3	0.4	0.2			14.8
2–5 cm	*456*	*84*	*19*	*32*	*591*	*559*
	81.6	15.0	3.4			100.0
	45.9	50.9	21.1			44.8
	36.5	6.7	1.5			44.8
5–10 cm	*308*	*63*	*39*	*35*	*445*	*410*
	75.1	15.4	9.5			100.0
	31.0	38.2	43.3			32.8
	24.7	5.0	3.1			32.8
More than 10 cm	*52*	*13*	*30*	*5*	*100*	*95*
	54.7	13.7	31.6			100.0
	5.2	7.9	33.3			7.6
	4.2	1.0	2.4			7.6
Other	*64*	*3*	*2*	*12*	*81*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*994*	*165*	*90*	–	*1336*	*1249*
	79.6	13.2	7.2			100.0
	100.0	100.0	100.0			100.0
	79.6	13.2	7.2			100.0

TABLE f_c 70 *Size of tumor* versus *Status of the homolateral axillary lymph nodes.*

Size of tumor	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*31*	*15*	*4*	*144*	*6*	*200*	*194*
	16.0	7.7	2.1	74.2			100.0
	13.6	7.7	4.6	18.2			15.0
	2.4	1.2	0.3	11.1			15.0
2–5 cm	*102*	*60*	*26*	*390*	*13*	*591*	*578*
	17.6	10.4	4.5	67.4			100.0
	44.7	31.0	29.9	48.4			44.4
	7.8	4.6	2.0	30.0			44.4
5–10 cm	*75*	*99*	*32*	*222*	*17*	*445*	*428*
	17.5	23.1	7.5	51.9			100.0
	32.9	51.0	36.8	28.1			32.9
	5.8	7.6	2.5	17.0			32.9
More than 10 cm	*20*	*20*	*25*	*33*	*2*	*100*	*98*
	20.4	20.4	25.5	33.7			100.0
	8.8	10.3	28.7	5.3			7.6
	1.5	1.5	1.9	2.7			7.6
Other	*14*	*14*	*6*	*44*	*3*	*81*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*228*	*194*	*87*	*789*	–	*1336*	*1298*
	17.5	15.0	6.7	60.8			100.0
	100.0	100.0	100.0	100.0			100.0
	17.5	15.0	6.7	60.8			100.0

TABLE f_c 71 *Size of tumor* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Status of the supra- and infraclavicular lymph nodes			
Size of tumor	Considered to contain growth	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*3*	*197*	*200*	*3*
	100 0			100.0
	4 1			4 1
	4 1			4 1
2–5 cm	*17*	*574*	*591*	*17*
	100 0			100.0
	23 0			23 0
	23 0			23 0
5–10 cm	*26*	*419*	*445*	*26*
	100 0			100.0
	35 1			35 1
	35 1			35 1
More than 10 cm	*28*	*72*	*100*	*28*
	100 0			100.0
	37 8			37 8
	37 8			37 8
Other	*6*	*75*	*81*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*74*	–	*1336*	*74*
	100 0			100.0
	100.0			100 0
	100.0			100 0

TABLE f_c 72 *Size of tumor* versus *Clinical stage (International* TNM *classification).*

	Clinical stage (International TNM classification)						
Size of tumor	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*132*	*42*	*23*	*3*	–	*200*	*200*
	66 0	21 0	11 5	1 5			100 0
	34 9	26 0	3 2	4 5			15 0
	9 9	3 1	1 7	0 2			15 0
2–5 cm	*245*	*124*	*206*	*14*	*2*	*591*	*589*
	41 5	21 0	35 0	2 5			100.0
	65 1	74 0	28 7	21 2			44 4
	18 3	9 3	15 6	1 0			44 2
5–10 cm	–	–	*418*	*27*	–	*445*	*445*
			93 9	6 1			100.0
			57 2	40 9			33 3
			31 3	2 0			33 3
More than 10 cm	–	–	*78*	*22*	–	*100*	*100*
			78 0	22 0			100 0
			10 9	33 3			7 5
			5 8	1 6			7 5
Other	*32*	*15*	*25*	*3*	*6*	*81*	–
Totals whole series	*409*	*181*	*750*	*69*	*8*	*1417*	*1409*
Totals noticed data	*377*	*166*	*725*	*66*	–	*1336*	*1334*
	28 2	12 5	54 4	4 9			100 0
	100.0	100 0	100 0	100 0			100 0
	28 2	12 5	54 4	4 9			100 0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 73 *Size of tumor* versus *Histology of the axillary lymph nodes.*

Size of tumor	Histology of the axillary lymph nodes: Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Not more than 2 cm	*79*	*73*	*48*	*200*	*152*
	52.0	48.0			**100.0**
	20.6	11.8			15.3
	7.9	7.3			15.3
2–5 cm	*210*	*257*	*124*	*591*	*467*
	45.0	55.0			**100.0**
	55.1	41.7			46.5
	20.9	25.6			46.5
5–10 cm	*85*	*240*	*120*	*445*	*325*
	26.2	73.8			**100.0**
	22.2	38.6			32.4
	8.5	23.9			32.4
More than 10 cm	*8*	*49*	*43*	*100*	*57*
	14.0	86.0			**100.0**
	2.1	7.9			5.7
	0.8	4.9			5.7
Other	*20*	*33*	*28*	*81*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*382*	*619*	–	*1336*	*1001*
	38.1	61.9			**100.0**
	100.0	**100.0**			**100.0**
	38.1	61.9			**100.0**

TABLE fc 74 *Fixation to skin* versus *Nipple retraction.*

Fixation to skin	Nipple retraction: Nipple retraction	No nipple retraction	Other	Totals whole series	Totals noticed data
Incomplete skin fixation	*107*	*231*	*11*	*349*	*338*
	31.7	68.3			**100.0**
	27.2	24.8			25.5
	8.1	17.5			25.5
Complete skin fixation	*147*	*186*	*11*	*344*	*333*
	44.1	55.9			**100.0**
	37.4	20.0			25.2
	11.1	14.1			25.2
Skin fixation wide of tumor but not beyond breast area	*46*	*32*	*6*	*84*	*78*
	59.0	41.0			**100.0**
	11.7	3.4			5.9
	3.5	2.4			5.9
Skin not involved	*93*	*481*	*7*	*581*	*574*
	16.2	83.8			**100.0**
	23.6	51.8			43.5
	7.0	36.4			43.5
Other	*5*	*3*	*51*	*59*	–
Totals whole series	*398*	*933*	*86*	*1417*	*1331*
Totals noticed data	*393*	*930*	–	*1358*	*1323*
	29.7	70.3			**100.0**
	100.0	**100.0**			**100.0**
	29.7	70.3			**100.0**

TABLE f_c 75 *Fixation to skin* versus *Pectoral muscle fixation.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Fixation to skin	Pectoral muscle fixation: No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
Incomplete skin fixation	*261*	*65*	*10*	*13*	*349*	*336*
	77.7	19.3	3.0			100.0
	24.8	38.7	11.1			25.6
	19.9	5.0	0.8			25.6
Complete skin fixation	*225*	*54*	*45*	*20*	*344*	*324*
	69.4	16.7	13.9			100.0
	21.4	32.1	50.0			24.7
	17.2	4.1	3.4			24.7
Skin fixation wide of	*41*	*9*	*27*	*7*	*84*	*77*
tumor but not beyond	53.2	11.7	35.1			100.0
breast area	3.9	5.4	30.0			5.9
	3.1	0.7	2.1			5.9
Skin not involved	*526*	*40*	*8*	*7*	*581*	*574*
	91.7	7.5	0.9			100.0
	49.9	23.8	8.8			43.8
	40.1	3.1	0.6			43.8
Other	*5*	–	*2*	*52*	*59*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*1053*	*168*	*90*	–	*1358*	*1311*
	80.3	12.8	6.9			100.0
	100.0	100.0	100.0			100.0
	80.3	12.8	6.9			100.0

TABLE f_c 76 *Fixation to skin* versus *Status of the homolateral axillary lymph nodes.*

Fixation to skin	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
Incomplete skin	*64*	*43*	*23*	*216*	*3*	*349*	*346*
fixation	18.5	12.4	6.6	62.5			100.0
	27.6	21.3	24.7	26.8			25.9
	4.8	3.2	1.7	16.2			25.9
Complete skin	*57*	*73*	*34*	*171*	*9*	*344*	*335*
fixation	17.0	21.8	10.1	51.1			100.0
	24.6	36.1	36.6	21.1			25.1
	4.3	5.5	2.5	12.8			25.1
Skin fixation wide of	*13*	*17*	*23*	*26*	*5*	*84*	*79*
tumor but not beyond	16.5	21.5	29.1	32.9			100.0
breast area	5.6	8.4	24.7	3.2			5.9
	1.0	1.3	1.7	1.9			5.9
Skin not involved	*98*	*69*	*13*	*394*	*7*	*581*	*574*
	17.1	12.0	2.3	68.6			100.0
	42.2	34.2	14.0	48.9			43.1
	7.3	5.1	1.1	29.6			43.1
Other	*10*	*6*	–	*26*	*17*	*59*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*232*	*202*	*93*	*807*	–	*1358*	*1334*
	17.4	15.1	7.0	60.5			100.0
	100.0	100.0	100.0	100.0			100.0
	17.4	15.1	7.0	60.5			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 77 *Fixation to skin* versus *Status of the supra- and infraclavicular lymph nodes*

	Status of the supra- and infraclavicular lymph nodes			
Fixation to skin	Considered to contain growth	Other	Totals whole series	Totals noticed data
Incomplete skin fixation	*16*	*333*	*349*	*16*
	100 0			**100 0**
	20 3			20 3
	20 3			20 3
Complete skin fixation	*30*	*314*	*344*	*30*
	100 0			**100 0**
	38 0			38 0
	38 0			38 0
Skin fixation wide of tumor but not beyond breast area	*22*	*62*	*84*	*22*
	100 0			**100 0**
	27 8			27 8
	27 8			27 8
Skin not involved	*11*	*570*	*581*	*11*
	100 0			**100 0**
	14 0			14 0
	14 0			14 0
Other	*1*	*58*	*59*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*79*	–	*1358*	*79*
	100 0			**100.0**
	100.0			**100.0**
	100 0			**100.0**

TABLE fc 78 *Fixation to skin* versus *Clinical stage (International* TNM *classification).*

	Clinical stage (International TNM classification)						
Fixation to skin	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Incomplete skin fixation	*118*	*54*	*167*	*10*	–	*349*	*349*
	33 8	15 5	47 9	2 9			**100.0**
	30 6	31 6	22 9	15 4			25 7
	8 7	4 0	12 3	0 7			25 7
Complete skin fixation	–	–	*314*	*29*	*1*	*344*	*343*
			91 6	8 5			**100.0**
			42 9	44 6			25 3
			23 0	2 1			25 3
Skin fixation wide of tumor but not beyond breast area	–	–	*66*	*18*	–	*84*	*84*
			78 6	21 4			**100.0**
			9 1	27 7			6 2
			4 9	1 3			6 2
Skin not involved	*268*	*118*	*183*	*8*	*4*	*581*	*577*
	46 4	20 5	31 7	1 4			**100 0**
	69 4	68 4	25 1	12 3			42 8
	19 9	8 8	13 5	0 6			42 8
Other	*28*	*10*	*14*	*4*	*3*	*59*	–
Totals whole series	*414*	*182*	*744*	*69*	*8*	*1417*	*1409*
Totals noticed data	*386*	*172*	*730*	*65*	–	*1358*	*1353*
	28 6	12 9	53 7	4 7			**100 0**
	100.0	**100 0**	**100.0**	**100.0**			**100 0**
	28 6	12 9	53 7	4 7			**100 0**

TABLE f_c 79 *Fixation to skin* versus *Clinical stage (International* TNM *classification). Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Clinical stage (International TNM classification)							
Fixation to skin	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
Incomplete skin fixation	*118*	*54*	*70*	*97*	*10*	–	*349*	*349*
	33 8	15 5	20 1	27 8	2 9			100 0
	30 6	31 6	40 0	17 5	15 4			25 8
	8 7	4 0	5 2	7 2	0 7			25 8
Complete skin fixation	–	–	–	*314*	*29*	*1*	*344*	*343*
				91 6	8 5			100 0
				56 5	44 6			25 4
				23 2	2 1			25 4
Skin fixation wide of tumor but not beyond breast area	–	–	–	*66*	*18*	–	*84*	*84*
				78 6	21 4			100.0
				11 9	27 7			6 2
				4 9	1 3			6 2
Skin not involved	*268*	*118*	*105*	*78*	*8*	*4*	*581*	*577*
	48 0	21 6	15 6	13 3	1 5			100 0
	69 4	68 4	60 0	14 1	12 3			42 6
	19 8	8 7	7 7	5 7	0 7			42 6
Other	*28*	*10*	*9*	*5*	*4*	*3*	*59*	–
Totals whole series	*414*	*182*	*184*	*560*	*69*	*8*	*1417*	*1409*
Totals noticed data	*386*	*172*	*175*	*555*	*65*	–	*1358*	*1353*
	28 5	12 8	12 9	40 9	4 8			100 0
	100 0	100.0	100 0	100 0	100 0			100.0
	28 5	12 8	12 9	40 9	4 8			100.0

TABLE f_c 80 *Fixation to skin* versus *Histology of the homolateral axillary lymph nodes.*

	Histology of the homolateral axillary lymph nodes				
Fixation to skin	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Incomplete skin fixation	*108*	*160*	*81*	*349*	*268*
	40 3	59 7			100 0
	28 0	25 5			26 5
	10 7	15 8			26 5
Complete skin fixation	*55*	*180*	*109*	*344*	*235*
	23 4	76 6			100.0
	14 2	28 7			23 2
	5 4	17 8			23 2
Skin fixation wide of tumor but not beyond breast area	*6*	*37*	*41*	*84*	*43*
	14 0	86 0			100 0
	1 6	5 9			4 2
	0 6	3 7			4 2
Skin not involved	*217*	*250*	*114*	*581*	*467*
	47 6	52 4			100.0
	56 3	39 8			46 1
	21 4	24 6			46 1
Other	*16*	*25*	*18*	*59*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*386*	*627*	–	*1358*	*1019*
	38 1	61 9			100.0
	100.0	100 0			100.0
	38 1	61 9			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 81 *Nipple retraction* versus *Pectoral muscle fixation.*

	Pectoral muscle fixation					
Nipple retraction	No fixation	Incomplete fixation	Complete fixation	Other	Totals whole series	Totals noticed data
Nipple retraction	*286*	*58*	*44*	*10*	*398*	*388*
	73.7	14.9	11.3			100.0
	27.1	34.9	48.4			29.6
	21.8	4.4	3.4			29.6
No nipple retraction	*769*	*108*	*47*	*9*	*933*	*924*
	83.2	11.7	5.1			100.0
	72.9	65.1	51.6			70.4
	58.6	8.2	3.6			70.4
Other	*3*	*2*	*1*	*80*	*86*	–
Totals whole series	*1058*	*168*	*92*	*99*	*1417*	*1318*
Totals noticed data	*1055*	*166*	*91*	–	*1331*	*1312*
	80.4	12.7	6.9			100.0
	100.0	100.0	100.0			100.0
	80.4	12.7	6.9			100.0

TABLE f_c 82 *Nipple retraction* versus *Status of the homolateral axillary lymph nodes.*

	Status of the homolateral axillary lymph nodes						
Nipple retraction	Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
Nipple retraction	*62*	*72*	*39*	*220*	*5*	*398*	*393*
	15.8	18.3	9.9	56.0			100.0
	27.0	36.2	42.4	27.8			30.0
	4.7	5.5	3.0	16.7			30.0
No nipple retraction	*168*	*127*	*53*	*571*	*14*	*933*	*919*
	18.3	13.8	5.8	62.1			100.0
	73.0	63.8	57.6	72.2			70.0
	12.8	9.7	4.0	43.5			70.0
Other	*12*	*9*	*1*	*42*	*22*	*86*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*230*	*199*	*92*	*791*	–	*1331*	*1312*
	17.5	15.2	7.0	60.3			100.0
	100.0	100.0	100.0	100.0			100.0
	17.5	15.2	7.0	60.3			100.0

TABLE f_c 83 *Nipple retraction* versus *Status of the supra- and infraclavicular lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

	Status of the supra- and infraclavicular lymph nodes			
Nipple retraction	Considered to contain growth	Other	Totals whole series	Totals noticed data
Nipple retraction	*30*	*368*	*398*	*30*
	100 0			**100.0**
	39 5			39 5
	39 5			39 5
No nipple retraction	*46*	*887*	*933*	*46*
	100 0			**100.0**
	60 5			60 5
	60 5			60 5
Other	*4*	*82*	*86*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*76*	–	*1331*	*76*
	100 0			**100.0**
	100.0			**100.0**
	100 0			**100 0**

TABLE f_c 84 *Nipple retraction* versus *Clinical stage (International* TNM *classification).*

	Clinical stage (International TNM classification)						
Nipple retraction	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Nipple retraction	*61*	*28*	*275*	*34*	–	*398*	*398*
	15 3	7 0	69 1	8 5			**100.0**
	15 9	16 5	38 7	54 0			29 9
	4 6	2 1	20 7	2 6			29 9
No nipple retraction	*322*	*142*	*435*	*29*	*5*	*933*	*928*
	34 6	15 3	46 8	3 2			**100.0**
	84 1	83.5	61 3	46 0			70 1
	24 3	10.7	32 8	2 2			70 1
Other	*31*	*13*	*33*	*6*	*3*	*86*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	*383*	*170*	*710*	*63*	–	*1331*	*1326*
	28 9	12 8	53 5	4 7			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	28 9	12 8	53 5	4 7			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE fc 85 *Nipple retraction* versus *Clinical stage (International* TNM *classification). Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms.*

	Clinical stage (International TNM classification)							
Nipple retraction	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
Nipple retraction	*61*	*28*	*55*	*220*	*34*	–	*398*	*398*
	15 3	7 0	13 8	55 3	8 5			100 0
	15 9	16 5	31 8	41 0	54 0			30 0
	4 6	2 1	4 1	16 6	2 6			30 0
No nipple retraction	*322*	*142*	*118*	*317*	*29*	*5*	*933*	*928*
	34 7	15 3	12 7	34 2	3 1			100 0
	84 1	83 5	68 2	59 0	46 0			70 0
	24 3	10 7	8 9	23 9	2 2			70 0
Other	*31*	*13*	*11*	*22*	*6*	*3*	*86*	–
Totals whole series	*414*	*183*	*184*	*559*	*69*	*8*	*1417*	*1409*
Totals noticed data	*383*	*170*	*173*	*537*	*63*	–	*1331*	*1326*
	28 9	12 8	13 0	40 5	4 8			100 0
	100.0	100.0	100.0	100.0	100.0			100 0
	28 9	12 8	13 0	40 5	4 8			100.0

TABLE fc 86 *Nipple retraction* versus *Histology of the axillary lymph nodes.*

	Histology of the axillary lymph nodes				
Nipple retraction	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Nipple retraction	*70*	*206*	*122*	*398*	*276*
	25 4	74 6			100.0
	18 4	33 3			27 6
	7 0	20 6			27 6
No nipple retraction	*311*	*412*	*210*	*933*	*723*
	43 0	57 0			100.0
	81 6	66 7			72 4
	31 1	41 2			72 4
Other	*21*	*34*	*31*	*86*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*381*	*618*	–	*1331*	*999*
	38 1	61 9			100.0
	100.0	100.0			100.0
	38 1	61 9			100.0

TABLE f_c 87 *Pectoral muscle fixation* versus *Status of the homolateral axillary lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Pectoral muscle fixation	Status of the homolateral axillary lymph nodes: Single	Multiple	Fixed to one another or to other structures	Considered to contain no growth	Other	Totals whole series	Totals noticed data
No fixation	*176*	*146*	*55*	*668*	*13*	*1058*	*1045*
	16 8	14 0	5 2	64 0			100.0
	76 9	75 3	59 8	85 0			80.3
	13 6	11 2	4 2	51.3			80.3
Incomplete fixation	*33*	*28*	*16*	*89*	*2*	*168*	*166*
	19 9	16 9	9.6	53 6			100.0
	14 4	14 4	17.4	11.2			12 8
	2 5	2 2	1 2	6 9			12 8
Complete fixation	*20*	*20*	*21*	*29*	*2*	*92*	*90*
	22 2	22 2	23 3	32.3			100.0
	8 7	10 3	22 8	3 8			6 9
	1 5	1 5	1 7	2 2			6 9
Other	*13*	*14*	*1*	*47*	*24*	*99*	–
Totals whole series	*242*	*208*	*93*	*833*	*41*	*1417*	*1376*
Totals noticed data	*229*	*194*	*92*	*786*	–	*1318*	*1301*
	17 6	14 9	7 1	60 4			100.0
	100.0	100.0	100.0	100.0			100.0
	17 6	14 9	7 1	60 4			100.0

TABLE f_c 88 *Pectoral muscle fixation* versus *Status of the supra- and infraclavicular lymph nodes.*

Pectoral muscle fixation	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
No fixation	*46*	*1012*	*1058*	*46*
	100 0			100.0
	59.7			59.7
	59 7			59 7
Incomplete fixation	*12*	*156*	*168*	*12*
	100 0			100.0
	15 6			15 6
	15 6			15 6
Complete fixation	*19*	*73*	*92*	*19*
	100 0			100.0
	24 7			24 7
	24 7			24 7
Other	*3*	*96*	*99*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*77*	–	*1318*	*77*
	100 0			100.0
	100 0			100.0
	100 0			100.0

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 89 *Pectoral muscle fixation* versus *Clinical stage (International* TNM *classification).*

Pectoral muscle fixation	Clinical stage (International TNM classification)						
	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
No fixation	*380*	*165*	*478*	*32*	*3*	*1058*	*1055*
	36 0	15 7	45 3	3 0			**100.0**
	100 0	100 0	67 4	52 5			80 3
	28 9	12 5	36 4	2 4			80 3
Incomplete fixation	–	–	*157*	*11*	–	*168*	*168*
			93 5	6.5			**100.0**
			22 0	18.0			12 7
			11.9	0 8			12 7
Complete fixation	–	–	*74*	*18*	–	*92*	*92*
			80.4	19 6			**100.0**
			10 6	29 5			7 0
			5.6	1.4			7 0
Other	*30*	*14*	*42*	*8*	*5*	*99*	–
Totals whole series	*410*	*179*	*751*	*69*	*8*	*1417*	*1409*
Totals noticed data	*380*	*165*	*709*	*61*	–	*1318*	*1315*
	28 9	12.5	54 0	4 6			**100.0**
	100.0	**100.0**	**100.0**	**100.0**			**100.0**
	28 9	12.5	54 0	4 6			**100.0**

TABLE f_c 90 *Pectoral muscle fixation* versus *Histology of the axillary lymph nodes.*

Pectoral muscle fixation	Histology of the axillary lymph nodes				
	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
No fixation	*322*	*490*	*246*	*1058*	*812*
	39.7	60 3			**100.0**
	84 5	80 6			82.1
	32 6	49.5			82 1
Incomplete fixation	*46*	*78*	*44*	*168*	*124*
	37.1	62.9			**100.0**
	12.1	12 8			12 5
	4 7	7 9			12.5
Complete fixation	*13*	*40*	*39*	*92*	*53*
	24.5	75.5			**100.0**
	3 4	6.6			5.4
	1.3	4 0			5 4
Other	*21*	*44*	*34*	*99*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*381*	*608*	–	*1318*	*989*
	38 5	61.5			**100.0**
	100.0	**100.0**			**100.0**
	38 5	61.5			**100.0**

TABLE f_c 91 *Status of the homolateral axillary lymph nodes* versus *Status of the supra- and infraclavicular lymph nodes*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Status of the homolateral axillary lymph nodes	Status of the supra- and infraclavicular lymph nodes: Considered to contain growth	Other	Totals whole series	Totals noticed data
Single	*13*	*229*	*242*	*13*
	100 0			**100 0**
	16 9			16 9
	16 9			16 9
Multiple	*21*	*187*	*208*	*21*
	100 0			**100 0**
	27 3			27 3
	27 3			27 3
Fixed to one another or to other structures	*23*	*70*	*93*	*23*
	100 0			**100 0**
	29 9			29 9
	29 9			29 9
Considered to contain no growth	*20*	*813*	*833*	*20*
	100 0			**100 0**
	26 0			26 0
	26 0			26 0
Other	*3*	*38*	*41*	–
Totals whole series	*80*	*1337*	*1417*	*80*
Totals noticed data	*77*	–	*1376*	*77*
	100 0			**100 0**
	100 0			**100 0**
	100 0			**100 0**

TABLE f_c 92 *Status of the homolateral axillary lymph nodes* versus *Clinical stage (International TNM classification).*

Status of the homolateral axillary lymph nodes	Clinical stage (International TNM classification): Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Single	–	*98*	*127*	*15*	*2*	*242*	*240*
		40 8	52 9	6 3			**100 0**
		51 6	17 6	23 1			17 6
		7 3	9 2	1 1			17 6
Multiple	–	*50*	*146*	*12*	–	*208*	*208*
		24 0	70 2	5 8			**100 0**
		26 3	20 2	18 5			15 1
		3 6	10 6	0 9			15 1
Fixed to one another or to other structures	–	–	*77*	*16*	–	*93*	*93*
			82 9	17 2			**100 0**
			10 1	24 6			6 8
			5 5	1 2			6 8
Considered to contain no growth	*390*	*42*	*376*	*22*	*3*	*833*	*830*
	47 0	5 1	45 3	2 7			**100 0**
	100 0	22 1	52 2	33 9			60 6
	28 5	3 2	27 4	1 5			60 6
Other	*10*	*3*	*21*	*4*	*3*	*41*	–
Totals whole series	*400*	*193*	*747*	*69*	*8*	*1417*	*1409*
Totals noticed data	*390*	*190*	*726*	*65*	–	*1376*	*1371*
	28 5	14 1	52 7	4 7			**100.0**
	100.0	**100 0**	**100.0**	**100.0**			**100.0**
	28 5	14 1	52 7	4 7			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 93 *Status of the homolateral axillary lymph nodes* versus *Clinical stage (International* TNM *classification).*

Stage III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms.*

Status of the homolateral axillary lymph nodes	Clinical stage (International TNM classification)							
	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
Single	–	*98*	*26*	*101*	*15*	*2*	*242*	*240*
		40.8	10.8	42.1	6.3			100.0
		51.6	14.5	18.6	23.1			17.5
		7.3	2.0	7.2	1.1			17.5
Multiple	–	*50*	*40*	*106*	*12*	–	*208*	*208*
		24.0	19.2	51.0	5.8			100.0
		26.3	22.3	19.5	18.5			15.2
		3.6	2.9	7.7	0.9			15.2
Fixed to one another or to other structures	–	–		*77*	*16*	–	*93*	*93*
				82.9	17.2			100.0
				13.4	24.6			6.8
				5.6	1.2			6.8
Considered to contain no growth	*390*	*42*	*113*	*263*	*22*	*3*	*833*	*830*
	47.0	5.1	14.7	30.6	2.7			100.0
	100.0	22.1	63.1	48.5	33.9			60.5
	28.5	3.2	8.2	19.1	1.5			60.5
Other	*10*	*3*	*5*	*16*	*4*	*3*	*41*	–
Totals whole series	*400*	*193*	*184*	*563*	*69*	*8*	*1417*	*1409*
Totals noticed data	*390*	*190*	*179*	*547*	*65*	–	*1376*	*1371*
	28.5	14.1	13.1	39.7	4.7			100.0
	100.0	100.0	100.0	100.0	100.0			100.0
	28.5	14.1	13.1	39.7	4.7			100.0

TABLE f_c 94 *Status of the homolateral axillary lymph nodes* versus *Histology of the axillary lymph nodes.*

Status of the homolateral axillary lymph nodes	Histology of the axillary lymph nodes				
	Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Single	*35*	*158*	*49*	*242*	*193*
	18.1	81.9			100.0
	8.9	24.8			18.8
	3.4	15.4			18.8
Multiple	*26*	*146*	*36*	*208*	*172*
	15.1	84.9			100.0
	6.6	23.0			16.7
	2.5	14.2			16.7
Fixed to one another or to other structures	*1*	*58*	*34*	*93*	*59*
	1.7	98.3			100.0
	0.3	9.1			5.7
	0.1	5.6			5.7
Considered to contain no growth	*330*	*274*	*229*	*833*	*604*
	54.6	45.4			100.0
	84.1	43.1			58.7
	32.1	26.6			58.7
Other	*10*	*16*	*15*	*41*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*392*	*636*	–	*1376*	*1028*
	38.1	61.9			100.0
	100.0	100.0			100.0
	38.1	61.9			100.0

TABLE f_c 95 *Status of the supra- and infraclavicular lymph nodes* versus *Clinical stage (International* TNM *classification).*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Status of the supra- and infraclavicular lymph nodes	Clinical stage (International TNM classification)						
	Stage I	Stage II	Stage III	Stage IV	Other	Totals whole series	Totals noticed data
Considered to contain growth	–	–	*66*	*14*	–	*80*	*80*
			82.5	17.5			**100.0**
			100.0	100.0			100.0
			82.5	17.5			100.0
Other	*414*	*183*	*677*	*55*	*8*	*1337*	–
Totals whole series	*414*	*183*	*743*	*69*	*8*	*1417*	*1409*
Totals noticed data	–	–	*66*	*14*	–	*80*	*80*
			82.5	17.5			**100.0**
			100.0	**100.0**			**100.0**
			82.5	17.5			**100.0**

TABLE f_c 96 *Status of the supra- and infraclavicular lymph nodes* versus *Clinical stage (International* TNM *classification). Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms.*

Status of the supra- and infraclavicular lymph nodes	Clinical stage (International TNM classification)							
	Stage I	Stage II	Stage III large tumor only, no other symptoms	Stage III also other symptoms	Stage IV	Other	Totals whole series	Totals noticed data
Considered to contain growth	–	–	–	*66*	*14*	–	*80*	*80*
				82.5	17.5			**100.0**
				100.0	100 0			100.0
				82.5	17.5			100.0
Other	*414*	*183*	*184*	*493*	*55*	*8*	*1337*	–
Totals whole series	*414*	*183*	*184*	*559*	*69*	*8*	*1417*	*1409*
Totals noticed data	–	–	–	*66*	*14*	–	*80*	*80*
				82.5	17.5			**100.0**
				100.0	**100.0**			**100.0**
				82.5	17.5			**100.0**

Numbers
% Horizontal
% Vertical
% Totals noticed data

TABLE f_c 97 *Status of the supra- and infraclavicular lymph nodes* versus *Histology of the axillary lymph nodes*

Status of the supra- and infraclavicular lymph nodes	Histology of the axillary lymph nodes: Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Considered to contain growth	*5*	*38*	*37*	*80*	*43*
	11 6	88 4			**100.0**
	100 0	100 0			100 0
	11 6	88 4			100 0
Other	*397*	*614*	*326*	*1337*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*5*	*38*	–	*80*	*43*
	11 6	88 4			100 0
	100 0	**100 0**			**100 0**
	11 6	88 4			100 0

TABLE f_c 98 *Clinical stage (International* TNM *classification)* versus *Histology of the axillary lymph nodes*

Clinical stage (International TNM classification)	Histology of the axillary lymph nodes: Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Stage I	*199*	*117*	*98*	*414*	*316*
	63 0	37 0			**100.0**
	49 6	18 0			30 1
	19 0	11 2			30 1
Stage II	*51*	*112*	*20*	*183*	*163*
	31 3	68 7			**100.0**
	12 7	17 3			15 6
	4 8	10 7			15 6
Stage III	*147*	*398*	*198*	*743*	*545*
	27 0	73 0			**100 0**
	36 7	61 2			51 8
	13 9	37 9			51 8
Stage IV	*4*	*22*	*43*	*69*	*26*
	15 4	84 6			**100.0**
	1 0	3 5			2 5
	0 4	2 1			2 5
Other	*1*	*3*	*4*	*8*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*401*	*649*	–	*1409*	*1050*
	38 1	61 9			**100 0**
	100.0	**100 0**			**100.0**
	38 1	61 9			**100.0**

TABLE f_c 99 *Clinical stage (International* TNM *classification). Stage* III *is divided into two groups, a: large tumor only, no other symptoms; b: also other symptoms,* versus *Histology of the axillary lymph nodes.*

Numbers
% Horizontal
% Vertical
% Totals noticed data

Clinical stage (International TNM classification)	Histology of the axillary lymph nodes: Histologically negative	Histologically positive	Other	Totals whole series	Totals noticed data
Stage I	*199*	*117*	*98*	*414*	*316*
	63.0	37.0			100.0
	49.6	18 0			30.1
	19 0	11 1			30.1
Stage II	*51*	*112*	*20*	*183*	*163*
	31.3	68.7			100.0
	12.7	17 3			15.5
	4.9	10 7			15.5
Stage III large tumor only,	*43*	*100*	*41*	*184*	*143*
no other symptoms	30 1	69 9			100.0
	10 7	15 4			13 6
	4 1	9 5			13 6
Stage III also other	*104*	*298*	*157*	*559*	*402*
symptoms	25.9	74 1			100 0
	25 9	45 9			38 3
	9 9	28.4			38.3
Stage IV	*4*	*22*	*43*	*69*	*26*
	15 4	84 6			100 0
	1 0	3 4			2.5
	0 4	2 1			2 5
Other	*1*	*3*	*4*	*8*	–
Totals whole series	*402*	*652*	*363*	*1417*	*1054*
Totals noticed data	*401*	*649*	–	*1409*	*1050*
	38 2	61 8			100 0
	100 0	100 0			100 0
	38 2	61 8			100 0

PART II FIGURES TO BE USED IN COMPUTING THE CURATIVE OPERABILITY. TABLES O1-O8

Occurrence of local and/or regional recurrences and distant metastases, 5 years follow up and 10 years follow up (each clinical stage considered as 100 percent).

TABLE O 1 *5 years follow up.*

			Clinical stage (International TNM classification)				
			Stage I	Stage II	Stage III	Stage IV*	Totals
I	Local/regional recurrence	No	*120*	*61*	*351*	*40*	*572*
	and/or distant metastases	%	42 9	48 8	66 6	85 1	58 4
II	Local/regional recurrence						
	without simultaneous	No	*12*	*7*	*53*	*3*	*75*
	distant metastases	%	4 3	5 6	10 3	6 2	7 7
I	Distant	No	*108*	*54*	*298*	*37*	*497*
minus II	metastases	%	38 8	42 9	56 3	78 7	50 7
III	First signs of local/regional						
	recurrence and/or distant	No	*74*	*51*	*270*	*37*	*432*
	metastases within 3 years	%	26 4	40 8	51 2	78 7	44 1
IV	Local/regional recurrence						
	without simultaneous distant	No	*8*	*5*	*38*	*3*	*54*
	metastases within 3 years	%	2 9	4 0	7 2	6 2	5 5
III	**First signs of distant**						
minus IV	**metastases within 3 years**	No	*66*	*46*	*232*	*34*	*378*
	(Cf table O 3)	%	**23.7**	**36 5**	**43 9**	**72 3**	**38 6**
V	First signs of local/regional						
	recurrence and/or distant	No	*46*	*10*	*81*	*3*	*140*
	metastases after 4 years or later	%	16 4	8 0	15 4	6 2	14 3
VI	Local/regional recurrence						
	without simultaneous distant	No	*4*	*2*	*15*	—	*21*
	metastases after 4 years or later	%	1 4	1 6	2 8	—	2 1
V	First signs of distant metas-	No	*42*	*8*	*66*	*3*	*119*
minus VI	tases after 4 years or later	%	15 1	6 3	12 5	6 2	12 1
VII	No local/regional recurrence	No	*158*	*65*	*178*	*7*	*408*
	and/or distant metastases	%	57 1	51 2	33 4	14 9	41 6
I + VII	Whole series	No	*278*	*126*	*529*	*47*	*980*
	5 years follow up	%	100 0	100 0	100 0	100 0	100 0

* Stage IV occurrence of new signs of tumor growth

For example

Stage I 66 patients with first signs of distant metastases within 3 years This is 23 7% of 278 patients in stage I of the whole series

TABLE O 2 *10 years follow up.*

			Clinical stage (International TNM classification)				
			Stage I	Stage II	Stage III	Stage IV*	Totals
I	Local/regional recurrence	No.	*46*	*21*	*157*	*18*	*242*
	and/or distant metastases	%	50 5	55.3	75.1	94 7	67 8
II	Local/regional recurrence						
	without simultaneous	No	*4*	*2*	*29*	*1*	*36*
	distant metastases	%	4 4	5 3	13 9	5.3	10 1
I	Distant	No.	*42*	*19*	*128*	*17*	*206*
minus II	metastases	%	46 2	50 0	61 2	89 5	57 7
III	First signs of local/regional						
	recurrence and/or distant	No.	*28*	*17*	*115*	*17*	*177*
	metastases within 3 years	%	30 8	44.7	55 0	89 5	49 6
IV	Local/regional recurrence						
	without simultaneous distant	No.	*3*	*2*	*17*	*1*	*23*
	metastases within 3 years	%	3 3	5.3	8.1	5.3	6 4
III	**First signs of distant**						
minus IV	**metastases within 3 years**	No	*25*	*15*	*98*	*16*	*154*
	(Cf table O 4)	%	27.5	39.5	46.9	84.2	43.1
V	First signs of local/regional						
	recurrence and/or distant	No	*18*	*4*	*42*	*1*	*65*
	metastases after 4 years or later	%	19.8	10.5	20 1	5 3	18.2
VI	Local/regional recurrence						
	without simultaneous distant	No	*1*	—	*12*	—	*13*
	metastases after 4 years or later	%	1.1	—	5 7	—	3.6
V	First signs of distant metas-	No	*17*	*4*	*30*	*1*	*52*
minus VI	tases after 4 years or later	%	18 7	10 5	14 4	5 3	14 6
VII	No local/regional recurrence	No.	*45*	*17*	*52*	*1*	*115*
	and/or distant metastases	%	49 5	44 7	24 9	5 3	32 2
I + VII	Whole series	No	*91*	*38*	*209*	*19*	*357*
	10 years follow up	%	100.0	100.0	100.0	100.0	100.0

* Stage IV occurrence of new signs of tumor growth

For example

Stage I. 25 patients with first signs of distant metastases within 3 years. This is 27.5% of 91 patients in stage I of the whole series.

Estimation of curative operability on the basis of 'first signs of distant metastases within 3 years after starting treatment' by stage (each clinical stage and combination of stages (International TNM classification) considered as 100 percent).

TABEL O 3 *5 years follow up.*

Clinical Stage (International TNM classification)		Distant* metastases within 3 years	'Curative operability' %	$\frac{100}{\%}$
Stage I	No.	*66*		
	%	23.7	76.3	1.31
Stage II	No.	*46*		
	%	36.5	63.5	1.57
Stage III	No.	*232*		
	%	43.9	56.1	1.78
Stage I + II	No.	*112*		
	%	27.7	72.3	1.38
Stage II + III	No.	*278*		
	%	42.4	57.6	1.74
Stage I + II + III	No.	*344*		
	%	36.9	63.1	1.58
Whole series	No.	*378*		
Including stage IV	%	38.6	61.4	1.63

For example:

Stage I: 66 patients with distant metastases within 3 years. This is 23.7% of 278 patients in stage I of the whole series.

This means 23.7% 'curative inoperable' and 100.0 – 23.7 = 76.3% 'curative operable'.

$\frac{100}{76.3\%} = 1.31$ (Cf. Appendix: table $\frac{100}{\%}$)

TABLE O 4 *10 years follow up.*

Clinical stage (International TNM classification)		Distant* metastases within 3 years	'Curative operability' %	$\frac{100}{\%}$
Stage I	No.	*25*		
	%	27.5	72.5	1.38
Stage II	No.	*15*		
	%	39.5	60.5	1.65
Stage III	No.	*98*		
	%	46.9	53.1	1.88
Stage I + II	No.	*40*		
	%	31.0	69.0	1.45
Stage II + III	No.	*113*		
	%	45.7	54.3	1.84
Stage I + II + III	No.	*138*		
	%	40.8	59.2	1.69
Whole series	No.	*154*		
Including Stage IV	%	43.1	56.9	1.76

* local and/or regional recurrence without simultaneous distant metastases are not considered.

Prognosis (in absolute and relative frequencies) by stage (each clinical stage considered as 100 percent).

TABLE O 5 *5 years follow up.*

Clinical Stage (International TNM classification)		Alive without signs of tumor	Alive with signs of tumor	**Died of tumor within 3 years** (Cf table O7)	Died of tumor after 4 years or later	Death from cause other than tumor or unknown	Totals
Stage I	No	*140*	*10*	*59*	*49*	*20*	*278*
	%	50 4	3 6	**21.2**	17 6	7 2	**100.0**
Stage II	No	*53*	*5*	*40*	*15*	*13*	*126*
	%	42 1	4 0	**31.7**	11 9	10 3	**100.0**
Stage III	No	*132*	*8*	*226*	*110*	*53*	*529*
	%	25 0	1 5	**42.7**	20 8	10 0	**100.0**
Stage IV	No	–	–	*41*	*4*	*2*	*47*
	%	–	–	**87.2**	8 5	4 3	**100.0**
Whole series	No	*325*	*23*	*366*	*178*	*88*	*980*
5 years follow up	%	33 3	2 2	**37 3**	18 2	9 0	**100.0**

TABLE O 6 *10 years follow up.*

Clinical Stage (International TNM classification)		Alive without signs of tumor	Alive with signs of tumor	**Died of tumor within 3 years** (Cf table O8)	Died of tumor after 4 years or later	Death from cause other than tumor or unknown	Totals
Stage I	No	*39*	*1*	*24*	*21*	*6*	*91*
	%	42 9	1 1	**26.4**	23 1	6 6	**100.0**
Stage II	No	*14*	*2*	*14*	*4*	*4*	*38*
	%	36 8	5 3	**36.8**	10 5	10 5	**100.0**
Stage III	No	*42*	–	*97*	*54*	*16*	*209*
	%	20 1	–	**46.4**	25 8	7 7	**100 0**
Stage IV	No	*1*	–	*17*	*1*	–	*19*
	%	5 3	–	**89.5**	5 3	–	**100.0**
Whole series	No	*96*	*3*	*152*	*80*	*26*	*357*
10 years follow up	%	26 9	0 8	**42 6**	22 4	7 3	**100.0**

Estimation of the curative operability on the basis of 'died of tumor within 3 years after starting treatment' by stage (each clinical stage and combination of stages (International TNM classification) considered as 100 percent).

TABEL O 7 *5 years follow up.*

Clinical stage (International TNM classification)		Died of tumor within 3 years	'Curative operability' %	100 / %
Stage I	No.	*59*		
	%	21 2	78 8	1 27
Stage II	No	*40*		
	%	31.7	68 3	1 46
Stage III	No.	*226*		
	%	42 7	57 3	1 75
Stage I + II	No	*99*		
	%	24 5	75 5	1 32
Stage II + III	No.	*266*		
	%	40 5	59 5	1 68
Stage I + II + III	No.	*325*		
	%	34 7	65 3	1 53
Whole series	No.	*366*		
Including stage IV	%	37 3	62 7	1 59

For example:

Stage I. 59 patients died of tumor within 3 years. This is 21 2% of 278 patients in stage I of the whole series. This means 21 2% 'curative inoperable' and 100.0 — 21.2 = 78 8% 'curative operable'.

$\frac{100}{78.8\%} = 1\ 27$ (Cf Appendix: table $\frac{100}{\%}$).

TABEL O 8 *10 years follow up.*

Clinical stage (International TNM classification)		Died of tumor within 3 years	'Curative operability'* %	100 / %
Stage I	No.	*24*		
	%	26 4	73 6	1 36
Stage II	No.	*14*		
	%	36.8	63 2	1 58
Stage III	No	*97*		
	%	46 4	53 6	1 87
Stage I + II	No	*38*		
	%	29 5	70 5	1 42
Stage II + III	No.	*111*		
	%	44 9	55 1	1 81
Stage I + II + III	No.	*135*		
	%	39.9	60.1	1 66
Whole series	No.	*152*		
Including stage IV	%	42 6	57.4	1 74

* Cf Fig. III-1.

PART III FIGURES TO BE USED IN COMPUTING THE NUMBER OF MEMBERS OF THE GENERAL FEMALE POPULATION REQUIRED FOR A CLINICAL TRIAL

TABLE P *Our computation of factor P on the basis of the annual number of deaths from malignant disease of the breast in females (modification from Segi, 1966).*

Country	Female population	Number of deaths from malignant disease of the breast	Percentage of deaths from malignant disease of the breast	Factor P $(\frac{100}{\%})$
Canada	9,361,600	2,353	0 025	$4\,0 \times 10^3$
Chile	4,194,413	291	0 007	$14\,2 \times 10^3$
USA (white)	84,538,000	21,985	0 026	$3\,9 \times 10^3$
USA (non-white)	11,367,000	2,020	0 017	$5\,9 \times 10^3$
Israel	1,043,061	258	0 025	$4\,0 \times 10^3$
Japan	48,925,000	1,857	0 0038	26×10^3
Germany (Federal republic)	30,361,700	8,389	0 028	$3\,6 \times 10^3$
Austria	3,824,644	1,048	0 027	$3\,7 \times 10^3$
Belgium	4,757,001	1,576	0 033	$3\,0 \times 10^3$
Denmark	2,361,217	873	0 037	$2\,7 \times 10^3$
Finland	2,351,061	351	0 015	$0\,67 \times 10^3$
France	24,424,823	6,305	0 026	$3\,9 \times 10^3$
Ireland	1,414,674	399	0 028	$3\,6 \times 10^3$
Italy	26,269,077	5,354	0 020	$5\,0 \times 10^3$
Norway	1,839,649	495	0 027	$3\,7 \times 10^3$
The Netherlands	6,003,373	1,819	0 030	$3\,3 \times 10^3$
Portugal	4,735,900	662	0 014	$7\,1 \times 10^3$
England and Wales	24,193,700	9,442	0.040	$2\,5 \times 10^3$
Scotland	2,705,200	975	0 036	$2\,8 \times 10^3$
Northern Ireland	741,000	185	0 025	$4\,0 \times 10^3$
Sweden	3,810,352	1,179	0 031	$3\,2 \times 10^3$
Switzerland	2,973,900	905	0 030	$3\,3 \times 10^3$
Australia	5,409,783	1,278	0 024	$4\,2 \times 10^3$
New Zealand	1,265,348	337	0,027	$3\,7 \times 10^3$

PART IV AIDS TO THE CALCULATION OF THE MULTIPLICATION-FACTOR $\frac{100}{\%}$

	0	*1*	*2*	*3*	*4*	*5*	*6*	*7*	*8*	*9*
0		1000 00	500 00	333 33	250 00	200 00	166 67	142 86	125 00	111 11
1	100 00	90 91	83 33	76 92	71 43	66 67	62 50	58 82	55 56	52 63
2	50 00	47 62	45 45	43 48	41 67	40 00	38 46	37 04	35 71	34 48
3	33 33	32 26	31 25	30 30	29 41	28 57	27 78	27 03	26 32	25 64
4	25 00	24 39	23 81	23 26	22 73	22 22	21 74	21 28	20 83	20 41
5	20 00	19 61	19 23	18 87	18 52	18 18	17 86	17 54	17 24	16 95
6	16 67	16 39	16 13	15 87	15 62	15 38	15 15	14 93	14 71	14 49
7	14.29	14 08	13 89	13 70	13 51	13 33	13 16	12 99	12 82	12 66
8	12 50	12 35	12 20	12 05	11 90	11 76	11 63	11 49	11 36	11 24
9	11 11	10 99	10 87	10 75	10 64	10 53	10 42	10 31	10 20	10 10
10	10 00	9 90	9 80	9 71	9 62	9 52	9 43	9 35	9 26	9 17
11	9 09	9 01	8 93	8 85	8 77	8 70	8 62	8 55	8 47	8 40
12	8 33	8 26	8 20	8 13	8 06	8 00	7 94	7 87	7 81	7 75
13	7 69	7 63	7 58	7 52	7 46	7 41	7 35	7 30	7 25	7 19
14	7 14	7 09	7 04	6 99	6 94	6 90	6 85	6 80	6 76	6 71
15	6 67	6 62	6 58	6 54	6 49	6 45	6 41	6 37	6 33	6 29
16	6 25	6 21	6 17	6 13	6 10	6 06	6 02	5 99	5 95	5 92
17	5 88	5 85	5 81	5 78	5 75	5 71	5 68	5 65	5 62	5 59
18	5 56	5 52	5 49	5 46	5 43	5 41	5 38	5 35	5 32	5 29
19	5 26	5 24	5 21	5 18	5 15	5 13	5 10	5 08	5 05	5 03
20	5 00	4 98	4 95	4 93	4 90	4 88	4 85	4 83	4 81	4 78
21	4 76	4 74	4 72	4 69	4 67	4 65	4 63	4 61	4 59	4 57
22	4 55	4 52	4 50	4 48	4 46	4 44	4 42	4 41	4 39	4 37
23	4 35	4 33	4 31	4 29	4 27	4 26	4 24	4 22	4 20	4 18
24	4 17	4 15	4 13	4 12	4 10	4 08	4 07	4 05	4 03	4 02
25	4 00	3 98	3 97	3 95	3 94	3 92	3 91	3 89	3 88	3 86
26	3 85	3 83	3 82	3 80	3 79	3 77	3 76	3 75	3 73	3 72
27	3 70	3 69	3 68	3 66	3 65	3 64	3 62	3 61	3 60	3 58
28	3 57	3 56	3 55	3 53	3 52	3 51	3 50	3 48	3 47	3 46
29	3 45	3 44	3 42	3 41	3 40	3 39	3 38	3 37	3 36	3 34
30	3 33	3 32	3 31	3 30	3 29	3 28	3 27	3 26	3 25	3 24
31	3 23	3 22	3 21	3 19	3 18	3 17	3 16	3 15	3 14	3 13
32	3 12	3 12	3 11	3 10	3 09	3 08	3 07	3 06	3 05	3 04
33	3 03	3 02	3 01	3 00	2 99	2 99	2 98	2 97	2 96	2 95
34	2 94	2 93	2 92	2 92	2 91	2 90	2 89	2 88	2 87	2 87
35	2 86	2 85	2 84	2 83	2 82	2 82	2 81	2 80	2 79	2 79
36	2 78	2 77	2 76	2 75	2 75	2 74	2 73	2 72	2 72	2 71
37	2 70	2 70	2 69	2 68	2 67	2 67	2 66	2 65	2 65	2 64
38	2 63	2 62	2 62	2 61	2 60	2 60	2 59	2 58	2 58	2 57
39	2 56	2 56	2 55	2 54	2 54	2 53	2 53	2 52	2 51	2 51
40	2 50	2 49	2 49	2 48	2 48	2 47	2 46	2 46	2 45	2 44
41	2 44	2 43	2 43	2 42	2 42	2 41	2 40	2 40	2 39	2 39
42	2 38	2 38	2 37	2 36	2 36	2 35	2 35	2 34	2 34	2 33
43	2 33	2 32	2 31	2 31	2 30	2 30	2 29	2 29	2 28	2 28
44	2 27	2 27	2 26	2 26	2 25	2 25	2 24	2 24	2 23	2 23
45	2 22	2 22	2 21	2 21	2 20	2 20	2 19	2 19	2 18	2 18
46	2 17	2 17	2 16	2 16	2 16	2 15	2 15	2 14	2 14	2 13
47	2 13	2 12	2 12	2 11	2 11	2 11	2 10	2 10	2 09	2 09
48	2 08	2 08	2 07	2 07	2 07	2 06	2 06	2 05	2 05	2 04
49	2 04	2 04	2 03	2 03	2 02	2 02	2 02	2 01	2 01	2 00

For example $\frac{100}{35\,6} = 2\,81$

	0	1	2	3	4	5	6	7	8	9
50	2 00	2 00	1 99	1 99	1 98	1 98	1 98	1 97	1 97	1 96
51	1 96	1 96	1 95	1 95	1 95	1 94	1 94	1 93	1 93	1 93
52	1 92	1 92	1 92	1 91	1 91	1 90	1 90	1 90	1 89	1 89
53	1 89	1 88	1 88	1 88	1 87	1 87	1 87	1 86	1 86	1 86
54	1 85	1 85	1 85	1 84	1 84	1 83	1 83	1 83	1 82	1 82
55	1 82	1 81	1 81	1 81	1 81	1 80	1 80	1 80	1 79	1 79
56	1 79	1 78	1 78	1 78	1 77	1 77	1 77	1 76	1 76	1 76
57	1 75	1 75	1 75	1 75	1 74	1 74	1 74	1 73	1 73	1 73
58	1 72	1 72	1 72	1 72	1 71	1 71	1 71	1 70	1 70	1 70
59	1 69	1 69	1 69	1 69	1 68	1 68	1 68	1 68	1 67	1 67
60	1 67	1 66	1 66	1 66	1 66	1 65	1 65	1 65	1 64	1 64
61	1 64	1 64	1 63	1 63	1 63	1 63	1 62	1 62	1 62	1 62
62	1 61	1 61	1 61	1 61	1 60	1 60	1 60	1 59	1 59	1 59
63	1 59	1 58	1 58	1 58	1 58	1 57	1 57	1 57	1 57	1 56
64	1 56	1 56	1 56	1 56	1 55	1 55	1 55	1 55	1 54	1 54
65	1 54	1 54	1 53	1 53	1 53	1 53	1 52	1 52	1 52	1 52
66	1 52	1 51	1 51	1 51	1 51	1 50	1 50	1 50	1 50	1 49
67	1 49	1 49	1 49	1 49	1 48	1 48	1 48	1 48	1 47	1 47
68	1 47	1 47	1 47	1 46	1 46	1 46	1 46	1 46	1 45	1 45
69	1 45	1 45	1 45	1 44	1 44	1 44	1 44	1 43	1 43	1 43
70	1 43	1 43	1 42	1 42	1 42	1 42	1 42	1 41	1 41	1 41
71	1 41	1 41	1 40	1 40	1 40	1 40	1 40	1 39	1 39	1 39
72	1 39	1 39	1 39	1 38	1 38	1 38	1 38	1 38	1 37	1 37
73	1 37	1 37	1 37	1 36	1 36	1 36	1 36	1 36	1 36	1 35
74	1 35	1 35	1 35	1 35	1 34	1 34	1 34	1 34	1 34	1 34
75	1 33	1 33	1 33	1 33	1 33	1 32	1 32	1 32	1 32	1 32
76	1 32	1 31	1 31	1 31	1 31	1 31	1 31	1 30	1 30	1 30
77	1 30	1 30	1 30	1 29	1 29	1 29	1 29	1 29	1 29	1 28
78	1 28	1 28	1 28	1 28	1 28	1 27	1 27	1 27	1 27	1 27
79	1 27	1 26	1 26	1 26	1 26	1 26	1 26	1 25	1 25	1 25
80	1 25	1 25	1 25	1 25	1 24	1 24	1 24	1 24	1 24	1 24
81	1 23	1 23	1 23	1 23	1 23	1 23	1 23	1 22	1 22	1 22
82	1 22	1 22	1 22	1 22	1 21	1 21	1 21	1 21	1 21	1 21
83	1 20	1 20	1 20	1 20	1 20	1 20	1 20	1 19	1 19	1 19
84	1 19	1 19	1 19	1 19	1 18	1 18	1 18	1 18	1 18	1 18
85	1 18	1 18	1 17	1 17	1 17	1 17	1 17	1 17	1 17	1 16
86	1 16	1 16	1 16	1 16	1 16	1 16	1 15	1 15	1 15	1 15
87	1 15	1 15	1 15	1 15	1 14	1 14	1 14	1 14	1 14	1 14
88	1 14	1 14	1 13	1 13	1 13	1 13	1 13	1 13	1 13	1 12
89	1 12	1 12	1 12	1 12	1 12	1 12	1 12	1 11	1 11	1 11
90	1 11	1 11	1 11	1 11	1 11	1 10	1 10	1 10	1 10	1 10
91	1 10	1 10	1 10	1 10	1 09	1 09	1 09	1 09	1 09	1 09
92	1 09	1 09	1 08	1 08	1 08	1 08	1 08	1 08	1 08	1 08
93	1 08	1 07	1 07	1 07	1 07	1 07	1 07	1 07	1 07	1 06
94	1 06	1 06	1 06	1 06	1 06	1 06	1 06	1 06	1 05	1 05
95	1 05	1 05	1 05	1 05	1 05	1 05	1 05	1 04	1 04	1 04
96	1 04	1 04	1 04	1 04	1 04	1 04	1 04	1 03	1 03	1 03
97	1 03	1 03	1 03	1 03	1 03	1 03	1 02	1 02	1 02	1 02
98	1 02	1 02	1 02	1 02	1 02	1 02	1 01	1 01	1 01	1 01
99	1 01	1 01	1 01	1 01	1 01	1 01	1 00	1 00	1 00	1 00

PART V INSERTION (MAMMA) FORM

No Clinical record: **Year:**

Clinic:
Date of admission: Physician:
Patient's marital state: unmarried/married/widowed/divorced.
Name of patient:
(can be omitted provided No. of clinical record is known)
Date of birth: male patient ☐
Profession of patient/husband:
Residence: Family Doctor:

History *(Tick appropriate box)*

Duration of symptoms:
First consultation of Family Doctor: Surgeon:
Commencement of treatment:

How was the tumor discovered:

a) Accidentally by patient	☐	Symptoms:	
b) Deliberate self-examination	☐	Tumor	☐
c) By periodic medical examination	☐	Pain	☐
d) Accidentally by physician	☐	Secretion	☐
e) With reference to breast complaints	☐	Discoloration	☐
f) With reference to other complaints (e.g.metastases)	☐	Swelling	☐

Year of menarche
Cycle _____ d /irregular ☐ disturbances:
w

Year of marriage(s)	1st	, 2nd	, 3rd	,	,	,	,
Dates of confinements	1st	, 2nd	, 3rd	,	,	,	,
Duration of nursing	1st	, 2nd	, 3rd	,	,	,	,
Puerperal mastitis	1st	, 2nd	, 3rd	,	,	,	,
Dates of abortions	1st	, 2nd	, 3rd	,	,	,	,

Year menopause castration ☐ operative ☐ X-Ray ☐

Mastopathia: none ☐ moderate ☐ serious ☐

Pregnant at time of discovery or treatment of tumor ☐
Nursing during discovery or treatment of tumor ☐
Other diagnoses:

Clinical findings *(draw in scheme) (Use of histological findings not allowed)*

Mammary tumor *(T)*

Occult tumor (T0) ☐
Tumor manifest ☐
Right ☐ Left ☐

Location (supine position)
- medial half . . . . . (170.1) . . . . . ☐
- lateral half . . . . . (170.2) . . . . . ☐
- subareolar (central) . (170.3) . . . . . ☐
- other localizations . . (170.4) . . . . . ☐
- not recorded . . . . (170.9) . . . . . ☐

Size
- biggest diameter 2 cm or less (T1) ☐
- „ „ 2–5 cm (T2) ☐
- „ „ 5–10 cm (T3) ☐
- „ „ more than 10 cm (T4) ☐

Consistency: soft ☐ elastic ☐ fluctuating ☐
solid ☐ hard ☐

Boundaries: sharp ☐ roonded ☐ vague ☐

Skin
- Skin not involved . . . . . (T1) ☐
- Incomplete fixation (limited movement or wrinkling) . . . . . (T2) ☐
- Complete fixation (infiltration, ulceration) or peau d'orange over tumor (T3) ☐
- Skin fixation wide of tumor but not beyond breast area . . . . . (T4) ☐

Paget's disease
- Limited to the nipple . . . . . (T1) ☐
- Outside the nipple . . . . . (T2) ☐

Nipple retraction
- Nipple retraction . . . . . (T2) ☐

Pectoral muscle fixation
- No fixation . . . . . (T1) ☐
- Incomplete fixation (contraction reduces mobility of tumor) . . . . . (T3a) ☐
- Complete fixation (contraction eliminates mobility of tumor) . . . . . (T3b) ☐

Chest wall attachment
- No fixation . . . . . (T1) ☐
- Fixation . . . . . (T4) ☐

Regional lymphnodes *(N)*

Homolateral lymphnodes
- Not palpable . . . . . (N0) ☐
- Palpable, still movable
  - Considered to contain no growth . . . . . (N1a) ☐
  - Considered to contain growth . . . . . (N1b) ☐
  - Single . . . . . (N1x) ☐
  - Multiple . . . . . (N1y) ☐
- Fixed to one another . . . . . (N2a) ☐
- Fixed to other structures . . . . . (N2b) ☐

Homolateral supra- or infraclavicular lymph nodes
- Movable or fixed . . . . . (N3) ☐

Arm edema
- Present . . . . . (N3) ☐

Distant metastases (M)

- No distant metastases . . . . . (M0) ☐
- Distant metastases:
  - Skin wide from breast . . . . . (M) ☐
  - Heterolateral lymphnodes or breast . . . . . (M) ☐
  - Lungs, pleura . . . . . (M) ☐
  - Bony metastases . . . . . (M) ☐
  - Liver . . . . . (M) ☐
  - Other sites . . . . . (M) ☐

Diameter cm

Boundaries

a) Sharp

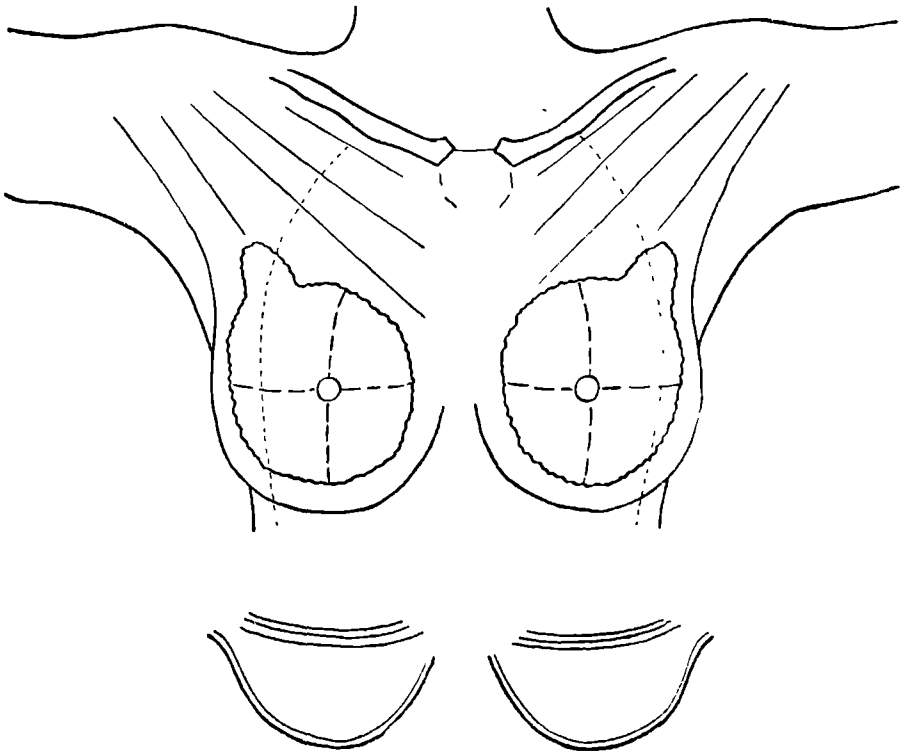
b) Diffuse

Relation to surroundings:

Ulceration

Ingrowth

Incomplete fixation



Staging

Carcinoma mammae $\frac{\text{right}}{\text{left}}$

T . . . . . }
N . . . . . } = Stage
M . . . . . }

Stage I - T1 N0 M0
- T2 N0 M0

Stage II - T1 N1 M0
- T2 N1 M0

Stage III - T1 N2 or N3 M0
- T2 N2 or N3 M0
- T3 N0, N1, N2 or N3 M0
- T4 N0, N1, N2 or N3 M0

Stage IV - Any combination of T and N with M

PART VI SOME STATISTICAL METHODS SUITABLE FOR THE ANALYSIS OFCONTROLLED CLINICAL TRIALS IN THE TREATMENT OF MAMMARY CARCINOMA

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1. *Introduction*

The purpose of clinical trials is to compare two or more methods of treating the same disease. By observing the statistical rules for adequate experimental design and for analyzing the findings, one attempts to obtain justified conclusions regarding the methods of treatment compared. In this appendix we discuss in some detail certain methods of analysis used in the study of the treatment of mammary carcinoma, and the corresponding experimental designs.

The decision as to which method of analysis is to be applied cannot be postponed until after the experiment, because the experimental design depends on the method of analysis employed. In this study we limit ourselves to methods of analyzing trials in which two treatments are compared, and which have the character of statistical tests. For every test there is a so-called 'Null Hypothesis' and a criterion on the basis of which the null hypothesis has to be rejected or accepted. In testing the results of a clinical trial, the null hypothesis is that the two methods of treatment are equivalent in a sense yet to be determined. The criterion consists of the comparison of a parameter to be calculated from the findings, the Statistic, with a so-called Critical Value. If the statistic is larger or smaller than the critical value, the null hypothesis is rejected and one concludes that the methods of treatment compared differ 'significantly'. In this study we shall always consider so-called Two-sided Tests which, if a significant difference is found between two methods of treatment, also offer the possibility of determining which was the better method of treatment. – The test criterion is selected in such a way that the probability of the decision that there *is* a difference between the therapies, if this decision is false, is below a previously determined limit, the level of significance α. As a rule, the tests are carried out with a level of significance $\alpha = 0.05 = 5\%$.

If a difference exists between the therapies, there is a certain probability that this will be detected by the test on the basis of the results of the trial, in other words that the null hypothesis will be rejected. This probability is a function of certain parameters in which the difference between the therapies is expressed. This function is called the Power of the test. One generally demands that the power for differences of at least a certain extent must exceed e.g. 95%. This can only be achieved when a certain minimum number of patients is used in the trial.

It is a condition of the validity of the conclusions of the statistical tests to be discussed that the methods of treatment are assigned to the patients at random. In order to maximize the power of the test with a given number of patients, the groups treated by

the two methods must be equal in size. If the patients become available gradually, they might for instance be treated alternately by the first and the second method, in order of their admission. In that case, however, it must be postulated that the order of admission is random in regard to elements which, apart from the treatment, might influence the course of their disease.

This assumption can be omitted if the order is determined in advance by drawing lots. This can be done as follows: if 400 patients are to be concerned in the trial, 200 will be treated by method A and 200 by method B. Two hundred numbers from the series 1, 2, ..., 400 are drawn by lot, e.g. by taking 200 cards at random from a box containing 400 numbered cards. The numbers drawn by lot then become the serial numbers of the patients to be treated by method A, while patients whose numbers are left in the box will be treated by method B. Tables with random numbers or certain computer programs (so-called Random Number Generators) may replace the box of cards for this purpose. This drawing of lots should preferably be done by a central organization not involved in the treatment. The physicians involved only learn what method to apply at the moment the patient starts treatment. This Lot method offers the advantage over the alternating assignment method that it is unpredictable, which may, for instance, prevent selection in accepting patients for treatment. For the sequential sign test discussed in Section 4 we need pairs of patients, one of whom is treated by method A and one by method B. We may compose these pairs of patients admitted immediately after one another, and we may by this experimental design also form pairs of patients similar in certain relevant elements, e.g. age. For every new patient we then check whether he 'fits' into an incomplete pair, if not, he becomes the first of a new pair. With both methods of pairing one must always determine by lot whether the patient admitted first is to be treated by method A or method B.

The most important points necessary from a statistical point of view for planning a clinical trial are listed above. They determine the statistical design of the experiment. During the trial, however, complications may arise in view of which one concludes, rightly or wrongly, that the design can no longer be followed. It is vitally important not to deviate from this design without consultation with the statistician involved in the organization of the trial. In Sections 2, 3 and 4 of this appendix we shall describe three tests applicable for the analysis of clinical trials in regard to mammary carcinoma. Special attention is given in this connection to the number of patients required. Since the supply of patients with mammary carcinoma per unit time is limited, and the effect of the treatment determined by the usual criteria (such as duration of survival) is not generally discovered until a considerable time later, the duration of the trial may be of greater importance in one's selection of method of analysis than the number of patients required. This aspect will be discussed further in Section 5.

2. *The χ^2 test for a 2 × 2 table*

Let us suppose that we are interested in comparing two methods of treatment, A and B. For the χ^2 test for a 2 × 2 table, the criterion of comparison can be described as follows. For every patient included in the trial we determine whether the treatment

applied has been 'successful'. It is designated successful if, after a certain period, previously stated conditions have been fulfilled. For instance, the patient must not have died or exhibited a recurrence. One must also define an 'unsuccessful' result: for instance if the patient has died from the mammary carcinoma during the period stated, or had a recurrence. In addition, there will be a number of patients to whom the terms 'successful' or 'unsuccessful' do not apply, for instance those who have died during the period in question due to accidents or other diseases. In our further discussion these 'undecided cases' will not be taken into consideration.

We now assume that we may logically speak of the probability P_A that 'success' will be obtained in a patient treated by method A. This is the case, for instance, when the patients included in the trial constitute a random sample of a population of patients of which a fraction P_A, after treatment by method A, will certainly be 'successful', or when every patient in such a population has a certain probability of 'success' after treatment by method A and the average of these individual probabilities is P_A. Similarly, we define P_B as the probability of 'success' of patients treated by method B.

Using the χ^2 test for a 2×2 table, we now test the null hypothesis $P_A = P_B$. For this test to be applied, the following parameters must be determined:

S_A = number of patients treated by method A (excepting undecided cases).

n_A = number of patients in whom method A was successful.

The terms S_B and n_B refer to method B.

For the sake of efficiency we generally attempt to have trials in which $S_A = S_B$, although 'drop-out' of patients may result in these numbers not being precisely the same at the end of the trial. If we further postulate that $N = S_A + S_B$ and $n = n_A + n_B$, then:

$$(1) \qquad \chi^2 = \frac{\{\,|n_A S_B - n_B S_A| - \tfrac{1}{2}N\,\}^2 N}{S_A S_B\, n\,(N - n)}$$

For the part of the equation between the vertical lines, the absolute value must be used.

We compare the statistic χ^2 with the critical value χ^2_α (of the χ^2 distribution with 1 degree of freedom) corresponding to the level of significance selected.

Some critical values are:

for $\alpha = 0.10$	(10%)	$\chi^2_{0.10} = 2.71$
$\alpha = 0.05$	(5%)	$\chi^2_{0.05} = 3.84$
$\alpha = 0.01$	(1%)	$\chi^2_{0.01} = 6.63$
$\alpha = 0.001$	(1‰)	$\chi^2_{0.001} = 10.83$

Let us assume that we test with $\alpha = 5\%$. We thus reject the null hypothesis $P_A = P_B$ if $\chi^2 > \chi^2_{0.05} = 3.84$. We may then conclude that $P_A \neq P_B$, i.e that the result of the trial is significant. This conclusion may be specified further.

The parameters:

$$\hat{P}_A = n_A/S_A \text{ and } \hat{P}_B = n_B/S_B$$

are, from the statistical point of view, 'estimates' of P_A and P_B. Thus, if with $\chi^2 > 3.84$ we also have $\hat{P}_A > \hat{P}_B$ (or $n_A S_B > n_B S_A$), we conclude that $P_A > P_B$ or that treatment A was significantly better than treatment B. With $\chi^2 > 3.84$ and $\hat{P}_A < \hat{P}_B$ (or $n_A S_B < n_B S_A$), the conclusion is that $P_A < P_B$, or that treatment B was significantly better than treatment A.

On the other hand, if we find that $\chi^2 < \chi^2_{0.05} = 3.84$, the hypothesis $P_A = P_B$ may not be rejected. We then conclude that the result of the trial was not statistically significant, or that the methods of treatment did not differ significantly.

If we have selected some different value for α, we must apply the corresponding critical value. Our formulation of the results may remain analogous in this case; it is advisable for the value of α chosen to be mentioned clearly by adding the qualification 'at the level of significance α' to all statements including the term 'significant'. This term without qualification is usually interpreted as 'significant for $\alpha = 5\%$'.

As a rule, in reporting the result of a test, the p value is also mentioned. This is the value that would have to be assigned to α for a just barely significant result. In the case considered here, the p value equals twice the probability that a random variable $\underline{u}$* with a standard normal distribution exceeds χ $(= \sqrt{\chi^2})$. The tables of normal distribution required for this purpose may be found in any statistical textbook or book of tables. If the p value is under 5%, the test result is significant for $\alpha = 5\%$ and vice versa. The more the p value deviates from the level of significance chosen, the greater the certainty with which the null hypothesis may be rejected or accepted.

An example is given here to illustrate the test.

A trial regarding mammary carcinoma was organized with 200 patients in group A and 200 in group B. In group A, 95 patients died of mammary carcinoma within 5 years, and 67 in group B. In addition, 18 patients dropped out of group A and 25 out of group B due to other causes within these 5 years.

The 2 × 2 table of the relevant data is then

Therapy	Treated	Of which: Successfully	Of which: Unsuccessfully
A	200 — 18 = 182	87	95
B	200 — 25 = 175	108	67
Total	357	195	162

consequently:

$S_A = 182$, $n_A = 87$ $\hat{P}_A = 87/182 = 47.8\%$

$S_B = 175$, $n_B = 108$ $\hat{P}_B = 108/175 = 61.7\%$

$N = 357$, $n = 195$ $N - n = 162$ and:

$$\chi^2 = \frac{\{\,|\,87 \times 175 - 108 \times 182\,| - \tfrac{1}{2} \times 357\,\}^2 \times 357}{182 \times 175 \times 195 \times 162} = 6.42$$

* In the text of this appendix symbols for random variables will be underlined.

Since this value is higher than 3.84, the hypothesis of equivalence at $\alpha = 5\%$ may be rejected. Since $\hat{P}_A < \hat{P}_B$, the conclusion is that treatment B was significantly better than treatment A. On the other hand if we had chosen $\alpha = 1\%$, the hypothesis of equivalence of the methods of treatment could not have been rejected, since $6.42 < 6.63$.

Further, $\chi = \sqrt{6.42} = 2.53$. From a table of standard normal distribution we find as the value for p:

$$p = 2P\,[\underline{u} > 2.53] = 1.1\%$$

Accordingly, $1\% < p < 5\%$, which agrees with what we found by comparing critical values.

The test described above is in fact an approximation to Fisher's exact rest for a 2×2 table. This approximation is sufficiently reliable in practice when the values of S_A, S_B, n and N-n are not too small (e.g. all $\geqq 10$). In clinical trials on mammary carcinoma this condition will generally be fulfilled. For exceptions, the reader is referred to the textbooks.

The power of the test is determined by the values of P_A and P_B. Eisenhart et al. (1947) present an approximation formula for this purpose based on the so-called arc sine transformation of the binominal distribution. This formula applies to the case $S_A = S_B = S$ which, as mentioned in Section 1, is the most efficient distribution of 2S patients over the treatment groups. If we now require that the power must equal $1-\beta$, we find an equation for the necessary number of patients S (in each of the two treatment groups) in order that for the given values of P_A and P_B rejection of the null hypothesis will be possible with a probability $1-\beta$ if the test is carried out with a level of significance of α. This equation is:

$$(2) \qquad S = \frac{(u_{\alpha/2} + u_\beta)^2}{2\,(\text{arc sine } \sqrt{P_A} - \text{arc sine } \sqrt{P_B})^2}$$

in which:

$u_{\alpha/2}$ and u_β are the values by which a variable with a standard normal distribution is exceeded with a probability of $\alpha/2$ or β (for $\alpha = \beta = 5\%$, $(u_{\alpha/2} + u_\beta)^2 = 13.0$).
Arc sine x is the angle in radials between $-\pi/2$ and $\pi/2$, the sine of which equals x (e.g. arc sine $0.5 = \pi/6$, because sine $\pi/6 =$ sine $30^\circ = 0.5$).

An example of the application of equation (2) would be as follows. The number of patients necessary with $\alpha = 5\%$ to obtain a significant result with 95% certainty ($\beta = 5\%$), if $P_A = 50\%$ and $P_B = 25\%$, is:

$$S = \frac{(1.9600 + 1.6449)^2}{2\,(\text{arc sine } \sqrt{0.50} - \text{arc sine } \sqrt{0.25})^2}$$

Since arc sine $\sqrt{0.50}$ = arc sine $\frac{1}{2}\sqrt{2} = 45^\circ = \pi/4$ (rad.) $= 0.7854$
and arc sine $\sqrt{0.25}$ = arc sine $\frac{1}{2} = 30^\circ = \pi/6$ (rad) $= 0.5236$

$$S = \frac{13.0}{2 \times 0.2618^2} = \frac{13.0}{0.1371} = 94.8$$

Accordingly, at least 95 patients are necessary per treatment group. Equation (2) is

approximately valid if α and β are relatively small (e.g. both less than 20%) and probabilities P_A and P_B do not differ too much. Naturally, it does not generally give a whole number for S. Since we need a minimum number to obtain a certain power of the test it is best to list the smallest whole number higher than the value of S found by equation (2).

In table S1 (cf. Ch. III p. 17) the necessary value for S is listed for combinations of P_A and P_B which are whole multiples of 10%, for $\alpha = \beta = 5\%$. On the basis of the above condition for the reliability of the approximation, a number of extreme combinations of P_A and P_B have been omitted.

The table shows a certain symmetry. If we exchange P_A and P_B, or exchange P_A and P_B for $(1 - P_A)$ and $(1 - P_B)$, we find the same number of patients is required.

Further, we find that the number of patients necessary depends to a great and non-linear extent on P_A and P_B; this renders interpolation between tabulated values impossible. For deviating values of P_A and P_B, equation (2) must be applied. The constants $u_{\alpha/2}$ and u_β for a few values of α and β can be found in the following table:

$u_{0.10} = 1.2816$
$u_{0.05} = 1.6449$
$u_{0.025} = 1.9600$
$u_{0.01} = 2.3263$
$u_{0.005} = 2.5758$

A simple table of the arc sine function can be found in e.g. Documenta Geigy (1960), p. 69.

Using equation (2) it is very easy to deduce a table from table S1 for other values of α and β; we have only to multiply by a factor:

$$\frac{(u_{\alpha/2} + u_\beta)^2}{(u_{0.025} + u_{0.05})^2} \approx \frac{(u_{\alpha/2} + u_\beta)^2}{13.0}$$

for $\alpha = 1\%$, $\beta = 1\%$	this factor equals 1.849
$\alpha = 1\%$, $\beta = 5\%$	,, ,, ,, 1.371
$\alpha = 5\%$, $\beta = 10\%$	,, ,, ,, 0.809

For $\alpha = 5\%$ and $\beta = 10\%$ this multiplication has been carried out (see table S2 cf. Ch. III, p. 18). As for this purpose, the rounded-off values of table S1 were used, direct calculation by equation (2) may reveal small deviations. Rümke (1968) published a table for the number of observations necessary for the one-sided χ^2 test (see Section 1) with $\alpha = \beta = 5\%$. This can also be used as a table for the two-sided test with $\alpha = 10\%$, $\beta = 5\%$. On verification we find that the values in this table are slightly higher than those calculated by equation (2). A slightly different approximation of the power of the test may have been used.

It can be concluded from table S1 that the number of observations necessary does not only depend on the difference between P_A and P_B. The question arises what number would be sufficient for every pair of values P_A, P_B with a given difference Δ to be demonstrated with a probability of at least $1-\beta$. We can find this number by substituting in equation (2) the values $P_A = \frac{1}{2}(1 + \Delta)$ and $P_B = \frac{1}{2}(1 - \Delta)$. A few examples are listed in table A1.

TABLE A1. *Power of the χ^2-test for a 2 × 2 table: level of significance $\alpha = 5\%$, equal sampel sizes S (number of patients in each therapy group).*

S_Δ = minimum number of patients required to detect with a probability of at least $1-\beta$ the difference between P_A and P_B if $|P_A - P_B| = \Delta$

$1-\beta_\Delta$ = minimum probability of detecting the difference between P_A and P_B and if the number of patients S is as indicated.

S_Δ	Δ	5%	10%	15%	20%	25%
	$1-\beta = 95\%$	2600	640	287	161	102
	$1-\beta = 90\%$	2100	524	232	130	83
$1-\beta_\Delta$	for S = 100	13.6%	28.2%	56.7%	81.3%	94.7%
	S = 200	23.0%	50.0%	85.4%	98.1%	99.9%
	S = 500	48.8%	87.1%	99.7%	100.0%	100.0%

Table A1 allows one to specify the conclusion further if the hypothesis $P_A = P_B$ cannot be rejected on the basis of the test. Suppose each treatment group includes more than 287 patients. According to table A1, the probability that the hypothesis $P_A = P_B$ will be rejected if the actual difference between P_A and P_B amounts to 15% is at least 95%. Therefore if (for $S \geq 287$) $P_A = P_B$ is not rejected, it may be concluded that the difference between P_A and P_B is not more than 15%. The probability of this conclusion if it is incorrect is less than 5%. – In table A1 we have listed for a few values of S the least power that can be achieved if P_A and P_B differ by an amount Δ. This gives us some impression of the power of the test when a certain required number cannot be obtained. If 95% certainty is required to demonstrate a difference of 10% in the probability of success, 648 patients per treatment group are necessary according to table A1. However, table A1 also shows that with only 200 patients per treatment group there is still a probability of at least 50% of detecting a difference of 10%, and that a difference of 20% will be established with almost complete certainty.

In using tables S1, S2 and A1, we must clearly recognize the significance of the parameters P_A and P_B. They concern unknown probabilities of success in applying the methods of treatment A and B to be compared, which must not be confused with the estimates of these probabilities $\hat{P}_A = n_A/S_A$ and $\hat{P}_B = n_B/S_B$ which can be obtained from observations after completion of the trial. It is quite possible that $\hat{P}_A$ and $\hat{P}_B$ will differ by less than 10% and that this difference will be significant according to the test, while the number of patients according to table A1 was insufficient to detect a difference of 10% between probabilities P_A and P_B with a certainty of 95% or 90%. If the number did fulfill this condition, we may still, if the null hypothesis is rejected, not conclude that P_A and P_B differ by at least 10%. Rejection of the null hypothesis only means that P_A and P_B are (probably) not equal. – In planning a trial it must also be kept in mind that the unknown probabilities P_A and P_B depend on the following factors:

1. criterion applied for 'success' of treatment. Instead of just establishing whether the patient has survived for a certain period since the start of treatment, one may also determine whether the patient had a recurrence during that period;
2. duration of period mentioned under 1; and
3. any selection applied to patients prior to their inclusion in the trial.

In this connection the following remarks must be made.

1. The criterion of 'success' must always be selected so that the treatment given to all patients fulfilling it may be considered more successful than that given to patients not fulfilling it.

2. It is possible for the difference between the short-term effects of two methods of treatment not to be the same as the difference between the long-term effects. This may be a reason for applying the test to e.g. the 5 year as well as the 10 year results. If we postulate an exponential distribution of durations of survival, we can calculate an optimal period as a function of the expected durations of survival per method of treatment. This aspect will not be further discussed here, the reader is referred to the example at the end of Section 3 of this appendix.

3. Let M be the population of all patients with mammary carcinoma on whom a clinical trial is to be carried out to compare therapeutical methods A and B. We will assume that M consists of two portions, M_0 and M_1, and that the difference in effect of the treatments given to M_1 is greater than that to M_0. The question then arises whether a trial limited to the patients in M_1 might not be more efficient than a trial without this limitation.

Let us suppose S_1 is the number of patients required per treatment for a trial limited to M_1 and that S is the number required for a trial within M. In this case S_1 will be less than S. If we further suppose that a fraction p_0 of the patients in M belong to portion M_0 and accordingly a fraction $(1-p_0)$ belong to M_1, it may be expected that among N patients of the entire population M there will be $(1-p_0)N$ patients of portion M_1. Consequently $N = S_1/(1-p_0)$ patients from M are needed in order that the expected number of patients from M_1 will be S_1. Now if this number N is less than S, we consider the trial within M_1 more efficient than a trial within M. In this respect, the following may be demonstrated (we refrain from giving the proof).

If within the partial population M_0 there is no difference in effect between methods of treatment A and B (i.e. if in M_0 the probabilities of success of A and B are the same), it is more efficient to limit the trial to the partial population M_1.

Example: Suppose that for the entire population M, $P_A = 0.6$ and $P_B = 0.5$. According to table S1, the number of patients S necessary per treatment group is then 642. The population consists of portions M_0 and M_1 containing fractions $p_0 = 0.2$ and $(1 - p_0) = 0.8$ of all patients of M. In M_0 the probabilities of success are: $P_{A0} = P_{B0} = 0.3$. If P_{A1} and P_{B1} are these probabilities for M_1 and P_A and P_B the probabilities for the entire population, then $P_A = p_0P_{A0} + (1 - p_0)\,P_{A1}$.

from which follows that $P_{A1} = \dfrac{P_A - p_0P_{A0}}{1 - p_0} = \dfrac{0.6 - 0.2 \times 0.3}{0.8} = 0.675$, similarly, we find that $P_{B1} = 0.55$.

Equation (2) then gives for the number of patients necessary for a trial within M, $(\alpha = \beta = 0.05)$:

$$S_1 = \frac{6.5}{(\text{arc sine } \sqrt{0.675} - \text{arc sine } \sqrt{0.55})^2} = 392.5$$

To attain an expected number of 392.5 patients from M_1 we need $N = 392.5/0.8 = 491$ patients of M. If the trial were not limited to M_1, 642 patients from M would have been

neccessary. Accordingly the trial within M_1 is in fact *more* efficient. In view of this it is advisable for all inoperable patients (a partial group M_0 with $P_{A0} = P_{B0} = 0$) to be excluded from the trial or, if operability can only be established after application of treatment, to exclude them from the calculations. However, this only applies when the criterion of inoperability is strictly independent of the treatment. If all patients who die within a certain period after operation are regarded as inoperable, this condition need not be fulfilled.

3. *Wilcoxon's two sample test*

In Wilcoxon's test the criterion of comparison is the period which elapses between commencement of treatment and occurrence of a certain eventuality, e.g. the patient's death or a recurrence. To simplify the terminology we call this period the patient's 'Survival Time'. The survival time is regarded in this connection as a random variable dependent on the treatment applied, indicated as $\underline{t}_A$ or $\underline{t}_B$. A random variable is a variable with a probability distribution. This means that for $\underline{t}_A$ for every value of $t \geqq 0$ the probability

$$F_A(t) = P[\underline{t}_A < t]$$

exists that a patient treated by method A will have a survival time less than t. The corresponding probability for t_B is expressed as:

$$F_B(t) = P[\underline{t}_B < t].$$

This assumption is realized for instance when the patients in the trial constitute a random sample from a population in which the cumulative frequency distribution of survival times (when all patients are treated by method A or B) is supplied by the function $F_A(t)$ or $F_B(t)$. The null hypothesis of Wilcoxon's test now implies that $\underline{t}_A$ and $\underline{t}_B$ have the same probability distribution, in other words that for each value of t,

$$F_A(t) = F_B(t) \tag{3}$$

applies.

The null hypothesis of the χ^2 test only requires that equation (3) applies to one particular value of t, the time until the result of the treatment is determined.

Wilcoxon's test is carried out as follows: wait until all patients have died and then arrange them according to increasing survival time. The result is expressed by a line of letters A and B, depending on whether the patient had been treated by method A or method B. In this line we then determine the number of times U where a letter A comes before (i.e. to the left of) a letter B. U then represents the number of pairs of one patient treated by method A and one by method B, in which the former had a shorter survival time than the latter. For S_A patients treated by method A and S_B treated by method B, we have:

$$0 \leqq U \leqq S_A S_B,$$

because $S_A S_B$ pairs of one A and one B can be formed. If the series includes such pairs with equal survival times, the contribution to the value U for each of these pairs equals $\frac{1}{2}$. Subsequently, we calculate the variable

$$(4) \qquad u = \frac{\{ \mid 2U - S_A S_B \mid - 1 \} \sqrt{3}}{\sqrt{S_A S_B (S_A + S_B + 1)}}$$

and reject the null hypothesis at the level of significance α, when $u > u_{\alpha/2}$. If $2U > S_A S_B$, we can conclude that the survival time of patients treated by method A was significantly shorter than that of patients treated by method B, i.e. that treatment B was better than treatment A. However, if $2U < S_A S_B$, we conclude that treatment A was significantly better than treatment B. If we find a value lower than $u_{\alpha/2}$, the null hypothesis cannot be rejected. In this case there is no significant difference between the survival times. The p value in Wilcoxon's test equals twice the probability that a variable with a standard normal distribution will exceed u. The procedure described above is an approximation of Wilcoxon's test, valid when the values of S_A and S_B are not too low and there are no excessively large ties, i.e. groups of patients with equal survival times. For the exact Wilcoxon's test and corrections for ties the reader is referred to textbooks on distribution free statistical methods.

Example:

Ten patients were treated by method A and 10 by method B. The survival times in years were:

A	1.6	2.2	2.5	3.2	3.8	4.1	4.9	5.0	5.7	8.3
B	0.4	0.6	1.1	1.2	1.7	2.2	2.4	2.5	3.1	4.0

The line of letters corresponding to increasing survival time now becomes:

B B B B A B AB B AB B A A B A A A A A
'tie' 'tie'

The number of letters A to the left of each letter B is now

0; 0; 0; 0; 1; $1\frac{1}{2}$; 2; $2\frac{1}{2}$; 3; 5

in which the letters A constituting a tie with a certain B as prescribed have been counted with this B as $\frac{1}{2}$. U is the sum of the line of numbers obtained, hence U = 15.

Further, $S_A = S_B = 10$; equation (4) now gives:

$$u = \frac{\{ \mid 30 - 100 \mid - 1 \} \sqrt{3}}{\sqrt{100 \times 21}} = \frac{69 \sqrt{3}}{10 \sqrt{21}} = 2.61.$$

This value is higher than $u_{0.01/2} = u_{0.005} = 2.5758$, so that the null hypothesis can be rejected for $\alpha = 5\%$ and for $\alpha = 1\%$. The p value is:

$$p = 2P [u > 2.61] = 0.009 = 0.9\%.$$

For calculating the number of patients required to achieve a certain power for the test, we once more start with equal numbers of patients per treatment group, $S_A = S_B = S$. Determination of this number is not as easy as for the χ^2 test. For this purpose

we apply the theorem that Wilcoxon's statistic $\underline{U}$ for a large total S has an approximately normal distribution, with expectation

$$\mu = S^2 P_{AB} \tag{5}$$

and variance

$$\sigma^2 = S^2 \{(P_{AAB} + P_{BBA} + 2P_{AB}P_{BA} - 1)\, S + 1 - P_{AAB} - P_{BBA} - P_{AB}P_{BA}\} \tag{6}$$

In this equiation, P_{AB} represents the probability that a patient treated by method A has a shorter survival time than one treated by method B, while P_{AAB} represents the possibility that two patients treated by method A will both have shorter survival times than one patient treated by method B. The definitions for $P_{BA} = (1 - P_{AB})$ and P_{BBA} are similar.

This theorem was first proved by Lehmann (1951): the formulae for μ and σ were deduced from ones supplied by van Dantzig (1951). If the null hypothesis (3) is correct, these can be expressed as:

$$\mu_0 = \tfrac{1}{2}S^2$$
$$\sigma_0^2 = \frac{1}{12}S^2\,(2S + 1)$$

Van Dantzig (1951) also indicates limits for $\frac{\sigma^2}{\sigma_0^2}$, which are useful in the subsequent calculation:

$$(\sqrt{3C + 1} - 1)^2 < \frac{\sigma^2}{\sigma_0^2} < \frac{3C}{2} \text{ with } C = 4P_{AB}P_{BA} \tag{7}$$

From (5) and (6) we can deduce that the number of patients per treatment group S necessary in a Wilcoxon test with level of significance α for the null hypothesis to be rejected with a probability of $(1 - \beta)$ can be found approximately by solving the equation:

$$S\,|\,P_{AB} - P_{BA}\,|\,\sqrt{3} - u_{\alpha/2}\sqrt{2S + 1} - u_{\beta}\sqrt{aS + b} = 0 \tag{8}$$

where $a = 12\,(P_{AAB} + P_{BBA} + 2P_{AB}P_{BA} - 1)$
and $b = 12\,(1 - P_{AAB} - P_{BBA} - P_{AB}P_{BA})$.

This equation has one positive root which in principle can be found by trial and error when variables P_{AB}, P_{AAB} and P_{BBA} are known. The approximation to the number S required found in this way is reasonably reliable when α and β are not too large (e.g. both $\leqq 20\%$) and P_{AB} is not too close to 0 or 1; in other words, for cases which do not give excessively low values for S.

The inequality given under (7) allows for calculation of limits of the necessary number of observations depending on P_{AB} $(= 1 - P_{BA})$ only. In combination with (8) this inequality leads to:

$$u_{\alpha/2} + u_{\beta}\,(\sqrt{3C + 1} - 1) < \tag{9}$$
$$< \frac{S}{\sqrt{2S + 1}}\,|\,P_{AB} - P_{BA}\,|\,\sqrt{3} < u_{\alpha/2} + u_{\beta}\sqrt{\frac{3C}{2}}$$

From this the limits of S can be deduced by solving two quadratic equations. In fig. 1 these limits are plotted for $\alpha = \beta = 5\%$ against

$$v = | P_{AB} - P_{BA} |^{-1}$$

Example. Suppose $P_{AB} =$ of 0.4; therefore $P_{BA} = 0.6$, i.e. the probability that the survival time of a patient treated by method A will exceed that of one treated by B equals 0.6. Thus $| P_{AB} - P_{BA} |^{-1} = 5$. Fig. 1 shows that the limits of S then fall between about 210 and 260. Consequently we need at least 210 patients and at most 260 per treatment group to demonstrate such a difference in survival times for $\alpha = 5\%$, with 95% certainty.

The number of observations required (S) can further be determined if the type of distribution of survival time is specified in more detail. We shall consider two relevant distribution types:*

1. The survival times $\underline{t}_A$ and $\underline{t}_B$ are both distributed exponentially, i.e.:

$$(10) \qquad F_A(t) = P[\underline{t}_A < t] = 1 - e^{-t/\mu_A}; \qquad F_B(t) = P[\underline{t}_B < t] = 1 - e^{-t/\mu_B},$$

where $e = 2.718282$, the base of the natural logarithmic system and μ_A and μ_B are the mean survival times during the period considered. Variables $P_{AB} - P_{BA}$, a and b in equation (8) can all be expressed as in:

$$(11) \qquad v = \frac{\mu_A + \mu_B}{|\mu_A - \mu_B|} = \frac{1}{|P_{AB} - P_{BA}|}$$

The solution of this equation for $\alpha = \beta = 5\%$ then yields values for S approximately the same as those according to the lower limit in fig. 1.

2. The logarithms ($\underline{L}_A = \log \underline{t}_A$) and ($\underline{L}_B = \log \underline{t}_B$) of the survival times are both normally distributed with means of μ_A and μ_B respectively and the same standard deviation σ. Analogous to the exponential distribution, we can now solve equation (8), giving P_{AB} from:

$$(12) \qquad P_{AB} = P\left[\underline{L}_A < \underline{L}_B\right] = P\left[\underline{u} < \frac{\mu_B - \mu_A}{\sigma\sqrt{2}}\right].$$

The determination of P_{AAB} and P_{BBA} is more complicated. If we plot the solutions for $\alpha = \beta = 5\%$ against $v = | P_{AB} - P_{BA} |^{-1}$ we again find a curve practically coinciding with the lower limit in fig. 1.

Specification of distribution type also allows comparison with the χ^2 test. Suppose that t_0 is the period of reference after which the result of the treatment is evaluated by the χ^2 test. The case with probabilities of success P_A and P_B in the χ^2 test then corresponds to

$$P[\underline{t}_A < t_0] = 1 - P_A; \qquad P[\underline{t}_B < t_0] = 1 - P_B.$$

This means, with survival times of the exponential type

$$\mu_A = -t_0/e \log P_A \text{ and } \mu_B = -t_0/e \log P_B$$

* For the sake of simplicity we ignore the fact that larger classes of distributions correspond to both types mentioned, equivalent in regard to the power of Wilcoxon's test.

Accordingly (see (11))

$$(13) \qquad v = \left| \frac{\log P_A + \log P_B}{\log P_A - \log P_B} \right|$$

and if we assume logarithmically normal distributions as indicated above under 2:

$$(14) \qquad \frac{\mu_B - \mu_A}{\sigma} = u_{p_A} - u_{p_B}{}^*$$

In this way the number of observations S required for Wilcoxon's test in both cases can be found as a function of P_A and P_B. Tables A2 and A3 list these values for $\alpha = \beta = 5\%$ and for combinations of P_B and P_B which are whole multiples of 10%. Since the period of reference t_0 does not occur in formulae (13) and (14) these tables are valid for all values of t_0.

If we compare tables A2 and A3 we see that the difference in assumption concerning the type of distribution gives rise to a considerable difference in the required number of observations as functions of P_A and P_B. Further, we find that both tables A3 and S1 are symmetrical in regard to substitution of P_A and P_B by $(1 - P_A)$ and $(1 - P_B)$. This is not so in table A2, where high values of P_A and P_B lead to considerably lower values of S than in the corresponding cases in table A3.

The converse applies for low values for P_A and P_B. In both tables the number of patients required is lower than for the corresponding cases in table S1. Application of Wilcoxon's test therefore reduces the number of patients required, although to a total which still depends on the distribution type of the survival times. Once the distribution type of survival times is assumed to be known, we may attempt to improve the power of the χ^2 test by a more favorable choice of period of reference t_0. The combination $P_A = 0.6$, and $P_B = 0.4$ according to table S1 requires 161 patients per treatment group, but if we apply Wilcoxon's test with exponential distribution of survival time, only 104 patients are necessary according to table A3. The combination mentioned gives the following parameters for the exponential distributions:

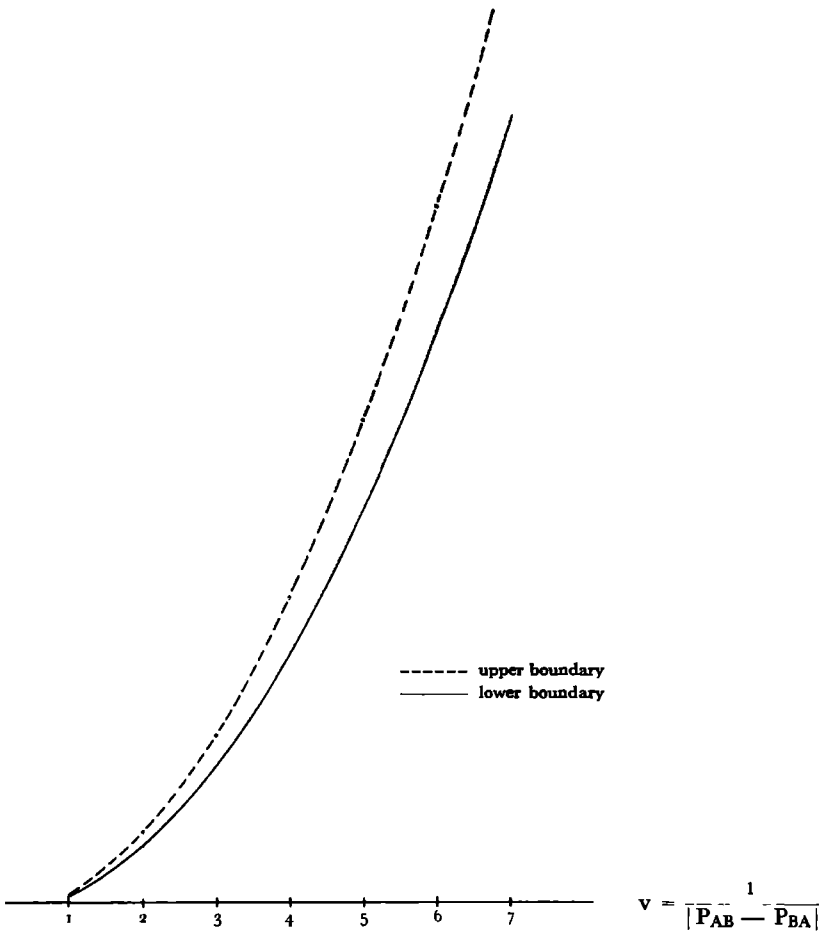
$$\mu_A = -\frac{t_0}{\log 0.6} = \frac{t_0}{0.51083} \text{ and } \mu_B = -\frac{t_0}{\log 0.4} = \frac{t_0}{0.91629}$$

If we choose a term of reference 2.357 t_0, the probabilities P_A and P_B become: $P'_A = e^{-2.357 \times 0.51083} = 0.3$ and $P'_B = e^{-2.357 \times 0.91629} = 0.1154$.
If we now calculate S according to equation (2) with these values for P_A and P_B, we find that S = 120. Consequently, if in calculating the number of patients for the χ^2 test we also assume the distribution type to be known, this number can be reduced considerably. In this respect the reduction in the number of patients required achieved by applying Wilcoxon's test as shown in tables A2 and A3 is presented as better than it actually is.

* Here, u_{P_A} is the value of the standard normal distribution with p value P_A (cf. definition of $u_{\alpha/2}$ and u_β under equation (2)).

er of Wilcoxon's two sample test
:l of significance $\alpha = 5\%$
al sample sizes S
ıdaries for the value of S required
detect with a difference between
$= P[\underline{t}_A < \underline{t}_B]$ and $P_{BA} = P[\underline{t}_A > \underline{t}_B]$
a probability of 95%.
boundaries are plotted as a function of

$$\frac{1}{|\overline{P}_{AB} - \overline{P}_{BA}|}$$



TABLES A2 AND A3

Power of Wilcoxon's two sample test: level of significance $\alpha = 5\%$, equal sample sizes S (= number of patients per treatment group). Minimum value of S required to detect with a probability of 95% the difference between probabilities of 'success' P_A and P_B after treatments A and B respectively. In this connection 'success' means a survival time of at least t_0 years; the value of S is independent of t_0.

TABLE A2: *The number S is calculated on the assumption that the survival times are exponentially distributed.*

P_A | P_B	10	20	30	40	50	60	70	80	90%
10		272	84	43	26	18	12	*	*
20	272		413	111	51	28	18	11	*
30	84	413		467	116	49	26	14	*
40	43	111	467		447	104	41	20	10
50	26	51	116	447		374	81	29	12
60	18	28	49	105	374		271	53	16
70	12	18	26	41	81	271		160	25
80	*	11	14	20	29	53	160		64
90	*	*	*	10	12	16	25	64	

TABLE A3: *The number S is calculated on the assumption that the logarithms of the survival times are normally distributed with equal standard deviation σ.*

P_A | P_B	10	20	30	40	50	60	70	80	90%
10		141	48	26	17	12	*	*	*
20	141		270	79	39	23	15	11	*
30	48	270		371	100	46	26	15	*
40	26	79	371		426	107	46	23	12
50	17	39	100	426		426	100	39	17
60	12	23	46	107	426		371	79	26
70	*	15	26	46	100	371		270	48
80	*	11	15	23	39	79	270		141
90	*	*	*	12	17	26	48	141	

* Values less than 10 omitted, because of possible lack of accuracy of normal approximation for distribution of U.

4. *Sequential sign tests*

Sequential tests are statistical procedures in which in principle one decides after each observation of an experiment whether more observations are to be made or whether the experiment may be terminated and a statistical conclusion drawn. The statistical conclusion is of the same character as described for the two previous tests; a certain null hypothesis is either accepted or rejected. The level of significance and the probability of

rejecting the null hypothesis, provided the actual situation includes at least some specified deviation from the null hypothesis, are established.

The tests described in Sections 2 and 3 were based on the two sample design in which the methods of treatment A and B are assigned at random to patients admitted in succession. Textbooks such as that by A. Wald (1947), P. Armitage (1960) and G.B. Wetherill (1966) contain no descriptions of sequential two sample tests. We shall therefore confine ourselves to sequential tests for the scheme with paired observations described at the end of Section 1. The observations in this instance are carried out on pairs of patients of whom one is treated by method A and one by method B. The conclusions are based exclusively on comparison of observations of paired patients with each other.

If this comparison is made at a certain interval of time after commencement of treatment, as with the χ^2 test, there are four possibilities:

1. both patients surviving;
2. both patients dead;
3. patient treated by method A still alive and the one treated by method B dead, or
4. patient treated by method B still alive and the one treated by method A dead.

The method based on these results is called the Sequential Test for Two Proportions. This test offers the advantage over methods still to be dicussed that it requires no assumptions concerning the nature of distributions of survival times. Nevertheless this method is not taken into account here because when it is applied a considerable proportion of pairs of patients (those who have both died or are both still alive) do not contribute to the decision, reducing the efficiency of the method. If we apply Student's sequential test, we determine for each pair of patients the difference in survival time between the patient treated by method A and the one treated by method B. This method presupposes that these differences or e.g. their logarithms are normally distributed, with the same standard deviation. Further, it has the disadvantage compared with the method discussed below that for each pair one has to wait until both patients are dead, which has an unfavorable effect on the duration of the experiment.

For these reasons we prefer a more detailed discussion of the Sequential Sign Tests. These tests are primarily intended for the following situation. An experiment consists of a series of comparisons of two objects A and B. These comparisons lead to 'preference for A' or 'preference for B'. For each comparison, the probability of a preference for A equals p and that of a preference for B equals $(1 - p)$. In this respect the sequential sign tests are tests for the null hypothesis $p = \frac{1}{2}$. Other decisive elements of the procedure are the level of significance and the requirement that the probability of rejection of the null hypothesis when $|p - \frac{1}{2}| > \delta > 0$ must be at least $(1 - \beta)$. Thus the test is determined by the values of the parameters α, δ and β.

In principle, the procedures are carried out as follows. After each comparison, one plots on a graph along the horizontal axis (drawn through the center) the number n of the preferences decided already, and along the vertical axis the excess d of the number of preferences for A over those for B. This number is thus positive in the event of a predominance of preferences for A and negative in the event of a predominance of preferences for B. By connecting the successive points we obtain a broken line graphically representing the progress of the experiment. This line begins at the origin. Each time a preference for A is reported, we progress one step obliquely upward to the right,

because n and d both increase by 1. In the event of a preference for B, we proceed one step obliquely down to the right, because in this case n increases by 1 but d is decreased by 1.

This line is called the Sample Path. The figure contains three more lines: the Upper Boundary U, the Lower Boundary L and the Middle Boundary M. If the sample path crosses the upper boundary, the experiment is terminated with the conclusion that there is a significant preference for A; if the sample path crosses the lower boundary, the experiment terminates with the conclusion that there is a significant preference for B, and if it crosses the middle boundary, the experiment ends in the conclusion that there is no significant difference in preferences. The length of the path projected onto the horizontal axis gives the number of comparisons of pairs necessary until the experiment could be terminated. This Required Number of Pairs is relatively low if there is a predominance of preferences in one direction. Prior to the experiment it is a random variable whose distribution is determined by the value of p.

Figure 2: Open Sequential Sign Test
Test for $p = 0.5$; level of significance $\alpha = 5\%$ (two-sided)
Power at least $1 - \beta = 95\%$ for $|p - 0.5| \geqq 0.15$
Sample path of experiment with $p = 2/3$ is drawn in the figure
p = probability of a preference for A ($= P_{BA}$).

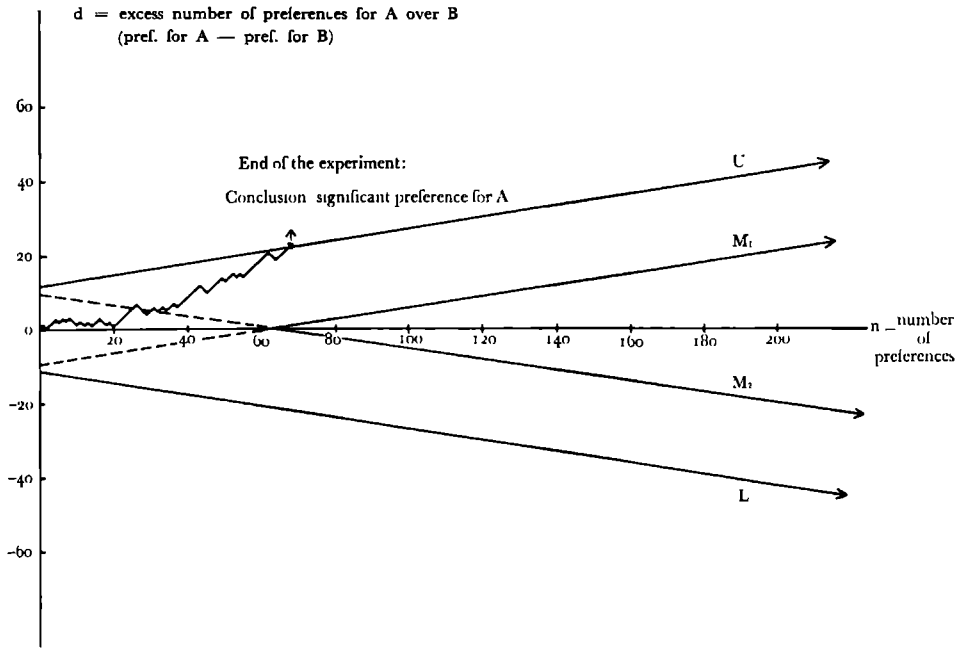


Figure 2 is a graph of an Open Sequential Sign Test. This test is an application of the principle for the construction of a two-sided sequential test described for a different case by M. Sobel and A. Wald (1949). It consists of the combination of two one-sided

(in this case, binominal) tests. The boundaries are straight lines given by the equations:

$$(15) \qquad \begin{array}{ll} U: d = a_1 + bn & M_1 : d = -a_2 + bn \text{ (for } d > o) \\ L: d = -a_1 - bn & M_2 : d = a_2 - bn \text{ (for } d < o) \end{array}$$

in which the coefficients a_1, a_2 and b are calculated from the parameters α, β and δ.

$$(16) \qquad a_1 = \frac{2 \log \frac{2(1-\beta)}{\alpha}}{\log \frac{1+2\delta}{1-2\delta}} \qquad a_2 = \frac{2 \log \frac{2-\alpha}{2\beta}}{\log \frac{1+2\delta}{1-2\delta}}$$

$$(17) \qquad b = \frac{-\log (1-4\delta^2)}{\log \frac{1+2\delta}{1-2\delta}}$$

In Figure 2, these boundaries have been drawn for $\alpha = \beta = 0.05$ (= 5%) and $\delta = 0.15$.

By substitution in equations (16) and (17) we get:

$$\log \frac{1+2\delta}{1-2\delta} = \log \frac{1.3}{0.7} = 0.26884$$

$$a_1 = \frac{2 \log \frac{1.9}{0.05}}{0.26884} = 11.75 \qquad a_1 = \frac{2 \log \frac{1.95}{0.1}}{0.26884} = 9.60$$

$$b = \frac{-\log 0.91}{0.26884} = 0.1524$$

In this figure we have also plotted the path of an experiment where $p = 2/3$, obtained by casting a dice and counting throws 1, 2, 3 and 4 as preferences for A and throws 5 and 6 as preferences for B. The experiment ended after 68 throws when the upper boundary was crossed, leading to the conclusion that there was a significant preference for A.

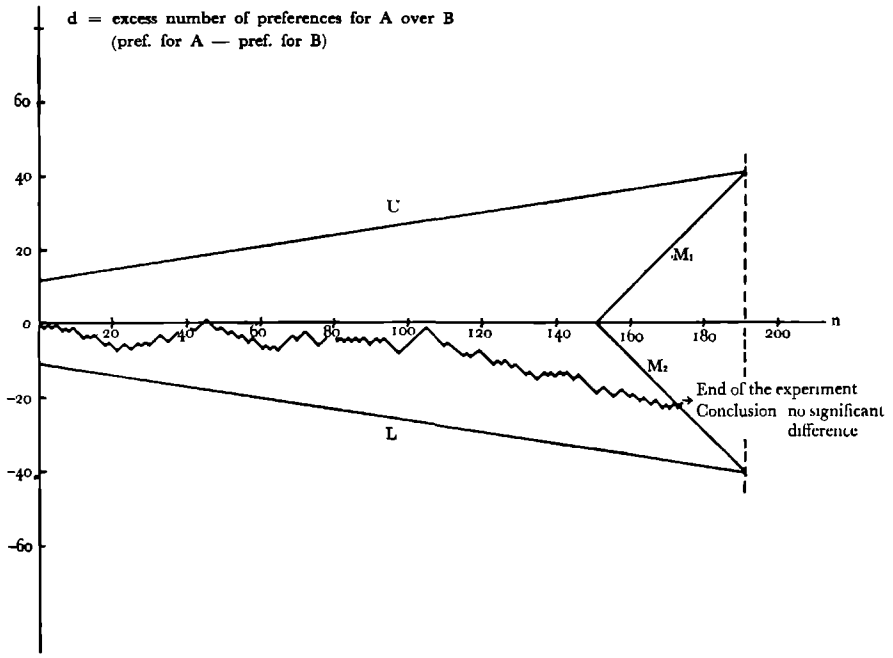
If the path successively crosses *both* extensions of the boundaries M_1 and M_2, indicated by dotted lines, this is equivalent to crossing one of these boundaries itself. This also leads to termination of the experiment with the conclusion that there is no significant difference in preferences. It can be demonstrated that the procedure will certainly end, although the delimitation of the scheme is open to the right. The probability that the sample path continues indefinitely in one of the corridors between U and M_1 or between L and M_2, equals 0. However, an objection to the open scheme is that it may be a long time before the experiment can be concluded, especially when the value of p is close to $\frac{1}{2}(1 + b)$ or $\frac{1}{2}(1 - b)$. For this reason, so-called Closed Sequential Designs have been elaborated, with a closed delimitation, so that a maximum can be indicated for the required number of preferences.

Figure 3 is the graph of Armitage's closed sequential design* for the same parameter values as the design in Figure 2. The boundaires U and L coincide with those of the open design, at least for $\delta \leqq 0.20$; the middle boundary here in the first instance is a

* See P. Armitage (1960), p. 34. In this connection he uses the term 'Restricted Designs', which we shall continue to use for his designs.

vertical line. Armitage has defined it in such a way that the requirements (the values of α, β and δ) are fulfilled.

Figure 3: Restricted sequential sign test (Armitage)
Test for p = 0.5; level of significance $\alpha = 5\%$ (two-sided)
Power at least $1 - \beta = 95\%$ for $| p - 0.5 | \geqq 0.15$
Sample path of experiment with p = 0.4 is drawn in the figure.
p = probability of a preference for A ($= P_{BA}$)



This was done by approximating the probability distribution of the sample path with the aid of a diffusion process, not discussed in detail here. In table A4 we show the maximum number of preferences required for a few combinations of α, β and δ.

TABLE A4: *Maximum number N of preferences required for Armitage's Restricted Sequential Sign Test, with level of significance α and minimum probability $(1 - \beta)$ of detecting values of p with $[p - 0.5] \geqq \delta$.* (From P. Armitage (1960), p. 35).

	value of N for:	
δ	$\alpha = \beta = 5\%$	$\alpha = 1\%$; $\beta = 5\%$
0.05	1778	2290
0.10	439	565
0.15	191	244
0.20	104	132

Subsequently this middle boundary may be replaced by two lines M_1 and M_2 at an angle of 45° to the horizontal axis, as shown in Figure 3. Once one of these lines has been crossed it is impossible for the sample path to reach the upper or lower boundaries, so the experiment may be terminated with the conclusion that no significant difference in preferences could be demonstrated.

Figure 3 shows the sample path of an experiment where $p = 0.4$, obtained by sampling from a table with random numbers and interpreting numbers 0, 1, 2 and 3 as preferences for A and numbers 5, 6, 7, 8, 9 as preferences for B.

This is an experiment which does not fulfil the null hypothesis ($p = 0.5$). Nevertheless the conclusion based on the sequential test after 172 comparisons of pairs is that there is no significant difference in preference, corresponding to $p = 0.5$. This is not surprising, since the design only guarantees adequate certainty (95%) for rejection of the null hypothesis when $| p - 0.5 | > 0.15$, i.e. for $p > 0.65$ or $p < 0.35$, which was not so in this experiment.

Besides Armitage's restricted design, there are other closed sequential designs, such as that of Bross (1952), also described in Armitage (1960), but they need not be discussed further. The sequential sign tests may be applied to the results of a clinical trial with pairs of patients of whom one is treated by method A and one by method B. A pair in which the patient treated by method A survives longer after commencement of treatment than the patient treated by method B is interpreted as a preference for A, and a pair with the opposite result as a preference for B. The probability p is then the probability $P_{BA} = P[\underline{t}_B < \underline{t}_A]$ introduced in Section 3.

In this instance the survival time after commencement of treatment is considered. Suppose that in one pair the patient receiving method A started treatment first. Now if the patient treated by method B dies first, the result of the pair may immediately be interpreted as a preference for A, but if the patient treated by method A dies first, the result may only be regarded as a preference for B if the patient treated by method B survives longer than the period between the commencements of treatment of both patients.

For a sequential sign test to be applied to the results of a clinical trial with pairs of patients, the distribution of the survival times $\underline{t}_A$ and $\underline{t}_B$ must fulfil a condition resulting from the fact that a considerable number of pairs of patients are involved simultaneously. In order for this situation to fit into the design for the sequential sign test, it is necessary that for every pair at any moment, i.e. irrespective of the length of time for which the pair has been included in the trial, the probability that the patient treated by method A has a longer survival time than the patient treated by method B remains constant.

This condition is only fulfilled if to $F_A(t) = P[\underline{t}_A < t]$ and $F_A(t) = P[\underline{t}_B < t]$ applies:

$$1 - F_B(t) = \{1 - F_A(t)\}^k \tag{18}$$

for a certain positive value of k and all values of t.

If condition (18) is fulfilled, k determines the value of p, for in this case we have:

$$p = P_{BA} = P[\underline{t}_B < \underline{t}_A] = \frac{1}{k+1} \tag{19}$$

The sequential sign tests are tests for the hypothesis $p = \frac{1}{2}$. If condition (18) is fulfilled, it follows from $p = \frac{1}{2}$ that $k = 1$ or $F_A(t) = F_B(t)$ for all positive values of t.

Consequently condition (18), which must be fulfilled if a sequential sign test is to be applied to the results of a pair trial, requires the null hypothesis that $\underline{t}_A$ and $\underline{t}_B$ have the same probability distribution. This is the same null hypothesis as in Wilcoxon's test, see (3).

A particularly important case concerns exponentially distributed survival times:

$$F_A(t) = 1 - e^{-t/\mu_A}; \qquad F_B(t) = 1 - e^{-t/\mu_B}$$

because then:

$$1 - F_B(t) = e^{-t/\mu_B} = (e^{-t/\mu_A})^{\mu_A/\mu_B} = \{1 - F_A(t)\}^k$$

with

$$k = \mu_A/\mu_B.$$

From this it follows (see (19)) that:

$$(20) \qquad P_{BA} = \frac{\mu_A}{\mu_A + \mu_B}.$$

For this particular case we have considered the numbers of patients required for the two sequential sign tests, indicated by OSST and ARST compared with those for the χ^2 test (CTTT) and Wilcoxon's test (WTST), see table A5.

1. As mentioned in the sequential sign tests the number of patients required is a random variable dependent on $p = P_{BA}$. For the open test we have mentioned the average numbers of pairs of patients required for the cases $p = 0.5$ and $|p - 0.5| = \delta$, as well as the maximum value of this average. For this purpose, use was made of table 3.1 in Armitage's book (1960). The (approximative) method for calculation of these averages was devised by Wald (1947). For Armitage's restricted test, the maximum number of pairs of patients required is listed; no average values were available here. The average number required is undoubtedly higher with the restricted test for $p = 0.5$ than for the open test. With $|p - 0.5| = \delta$ the difference will probably be slight.
2. For the sequential tests, the numbers of pairs required are listed; for the χ^2 test and Wilcoxon's test, the numbers of patients per treatment group. In both the number of patients necessary for a trial is double.
3. In the χ^2 test, the number required also depends on the period of reference t_0 (see also end of section 3). When μ_A and μ_B are given, the proportion of t_0 and $\bar{\mu} = \frac{1}{2}(\mu_A + \mu_B)$ is decisive. In the table, the numbers of patients necessary are listed for $t_0/\bar{\mu} = 1.0$, 1.5 and 2.0.

Table A5 shows that the open sequential test requires fewer patients on average than the χ^2 test and Wilcoxon's test if $|p - \frac{1}{2}| = \delta$, and *a fortiori* if $|p - \frac{1}{2}| > \delta$. This is probably also true of Armitage's test. In general, therefore, the sequential tests would appear to be more efficient than tests with a fixed number of random samples if the methods of treatment diverge widely. It is only when the methods of treatment are more or less equivalent that tests with a fixed number of random samples appear to be preferable. This would constitute a strong argument in favor of using one of the sequential sign tests. If the methods of treatment differ only slightly, there is less objection to including a few more patients in the trial. If, on the other hand the methods

of treatment are markedly different, the presence of a large number of patients in the trial implies that, purely for the sake of the trial, large numbers of patients are being treated by an inferior method.

TABLE A5: *Comparison between:*
OSST: *Open Sequential Sign Test*
ARST: *Armitage's Restricted Sequential Sign Test*
WTST: *Wilcoxon's Two Sample Test*
CTTT: χ^2 *Test for* 2×2 *table*
with respect to number of patients required.
Level of significance $\alpha = 5\%$; *required power for* $|p - 0.5| \geqq \delta$ *is* $\geqq 95\%$.
Survival times are assumed to be distributed exponentially.

	OSST			ARST	WTST	CTTT		
	Average number of pairs required			Maximum number of pairs required	Number required in each group	Number of patients required in each treatment group if $t_0/\bar{\mu} =$		
δ	$p = 0.5$	if $\lvert p - 0.5 \rvert = \delta$	at maximum			1.0	1.5	2.0
0.05	870	660	1080	1778	861	1108	1001	1036
0.10	215	160	270	439	210	271	247	257
0.15	95	70	115	191	91	116	107	113
0.20	51	40	63	104	49	62	59	63
0.25	31	25	38	62	30	37	36	40

$p = P_{BA} = P[\underline{t}_A > \underline{t}_B]$
t_0 = reference period for the CTTT
$\bar{\mu} = \frac{1}{2}(\mu_A + \mu_B)$, the average of the expected values of survival times.

There is, however, an important objection to this argument. For tests with a fixed number of samples, it is only necessary to collect patients until the previously fixed number is attained. With sequential tests, this number is not previously known and it is therefore necessary in principle to continue to include patients in the trial until it is concluded or at any rate until the large maximum number required for Armitage's test is reached. As a result, especially in trials with patients with long average survival times, large numbers of patients will be involved in the trials who do not contribute to the ultimate conclusion, and who are not taken into account in the calculations for table A5.

We can reduce this number of 'superfluous' patients by limiting the total included in the trial at the beginning to the number required on average in a favorable situation (e.g.: $|p - 0.5| = \delta$). More patients should only be included in the trial if it appears that the number required will be larger. This means a considerable delay in conclusion of the trial, since patient pairs introduced later will also yield their results later.

The period in which a trial is completed is, however, an important aspect of the design. As long as the trial has not resulted in a conclusion concerning the choice between methods of treatment, numerous patients not included in the trial risk being treated by a method which the trial will eventually prove inferior. This number of patients might well be much larger than the number of extra patients treated by the inferior method in a trial completed earlier due to the inclusion of a larger number of

patients. This consideration has prompted us to pay more attention to the relation between duration of trial and choice of test.

5. *Duration of trial*

We base our considerations re. duration of the trial on the following assumptions.

1. The survival times $\underline{t}_A$ and $\underline{t}_B$ are distributed exponentially with averages μ_A and μ_B respectively.
2. The intake of patients is homogeneous: on average, m pairs of patients can be formed per year, i.e. m patients per year can be included in each of the patient groups.
3. When tests with a fixed number of samples are applied, patients are included in the trial until the number required for the test has been attained.
4. When one of the sequential sign tests is used, inclusion of new patients in the trial is continued until the trial is complete.

An intake of patients is called 'homogeneous' if it neither increases nor decreases systematically with time. From the mathematical point of view the intake can follow a Poisson process in which the time intervals between successively admitted patients is distributed exponentially with a constant average.

We base our discussion on equation 7.2 (p. 84) in Armitage's book (1960). On the above assumptions 1, 2 and 4 it gives the expectation G of the number of pairs of which at least one patient has died when the trial has run for T years.

$$(21) \qquad G = mT\left\{1 - \frac{1 - e^{-2\bar{\lambda}T}}{2\bar{\lambda}T}\right\},$$

in which

$$\bar{\lambda} = \tfrac{1}{2}\left(\frac{1}{\mu_A} + \frac{1}{\mu_B}\right).$$

The determination of T, when G and m are given from (21), would require the solution of a transcendent equation. We therefore determine m as a function of G and T. We have done this for the open and the closed sequential sign tests and have substituted for G the maximum average number required and the maximum number of pairs of patients required respectively. Thus we find the number of pairs of patients m which must be available each year in order to obtain a number of results within a period T of the beginning of the trial sufficient on average (with the open sequential test) or sufficient (with the restricted test) for completion of the trial. The figures in question can be found in column OSST and ARST in table A6, where various cases are distinguished according to the value of $\delta = |\, P_{BA} - 0.5 \,|$, in which $P_{BA} = P[\underline{t}_B < \underline{t}_A] = \mu_A/(\mu_A + \mu_B) = \mu_A/(2\bar{\mu})$ (cf. (20)).

The length of time required for a trial analysed by the χ^2 test for a 2×2 table is the sum of:

1. the time t_1 necessary to obtain the required number of patients S per treatment group, and
2. the period of reference t_0.

Once the last patient has been included in the trial (after period t_1), we must wait for a further period t_0 until the results are known for this patient. For an intake of m patients per treatment group per year, $t_1 = S/m$, so that for the χ^2 test we find:

$$T = t_0 + S/m. \tag{22}$$

The number S under the assumptions 1 and 2 is a function of the relation between t_0 and $\bar{\mu} = \frac{1}{2}(\mu_A + \mu_B)$.

By substituting this value for S in equation (22), we can find m from (22) as a function of α, β, δ, $\bar{\mu}$, T and $t_0/\bar{\mu}$. This number m then represents the number of patients which must be available annually per treatment group in order to complete the trial within period T with application of the χ^2 test for a 2×2 table with period of reference t_0.

This number is presented in table A6 for $t_0/\bar{\mu} = 0.5$, 0.75 and 1.0. Clearly, in the majority of the cases m reaches its minimum for a value of $t_0/\bar{\mu}$ in this interval.

Table A6 contains no data concerning Wilcoxon's test, because with this test, the trial for all cases considered will generally last longer than the defined period T as Wilcoxon's statistic can only be calculated when all the patients of at least one treatment group have died.

TABLE A6: *Average intake m of patients for each therapy per year required to complete a clinical trial within T years at the average.*

			Value of m for				
			OSST[1]	ARST[2]	CTTT[3]		
T	$\bar{\mu}$	δ			$t_0/\bar{\mu} =$ 0 5	$t_0/\bar{\mu} =$ 0 75	$t_0/\bar{\mu} =$ 1 0
6	3	0 1	58 9	95 8	90 0	83 2	90 3
6	3	0 2	13 3	21 9	19 8	18 9	20 7
8	3	0 1	41 1	66 9	62 3	54 3	54 2
8	3	0 2	9 3	15 4	13.7	12 3	12 4
10	3	0 1	31 5	51 3	47 6	40 3	38 7
10	3	0 2	7 2	11 9	10 5	9 2	8 9
10	4	0 1	33 4	54 3	50 6	44 6	45 2
10	4	0 2	7 6	12 5	11.1	10 1	10.3
10	5	0 1	35 4	57 5	54 0	49 9	54 2
10	5	0 2	8 0	13 1	11 9	11 4	12 4

Level of significance $\alpha = 5\%$, required power $1 - \beta = 95\%$ for $P_{AB} - 0\,5 \mid \geqq \delta$ Survival distributions assumed to be exponential which expected values μ_A and μ_B, $\bar{\mu} = \frac{1}{2}(\mu_A + \mu_B)$

1 OSST (Open Sequential Sign Test), m computed from (21) with G = the maximum of the average number of pairs of patients required

2 ARST (Armitage's Restricted Sequential Sign Test), m computed from (21) with C = the maximum number of pairs of patients required

3 CTTT (χ^2 Test for 2×2 Table), m computed from (22) with S = the number of patients required for each therapy group according to formula (2)
t_0 = reference period for CTTT

As far as duration of the trial is concerned, we shall further restrict ourselves to comparing the sequential tests and the χ^2 test for a 2×2 table on the basis of table A6.

On this basis we are inclined to prefer the sequential method to the χ^2 test. With the

open sequential test the maximum average intake of patients required per year is considerably less; with the restricted test the maximum intake required is only slightly higher than that required with the χ^2 test. This means that when the conditions stated at the beginning of this section are observed, the sequential tests will, given a certain intake of patients, generally give a result earlier than the χ^2 test.

Some notes must be made in this connection.

1. The methods are compared exclusively for the case of exponentially distributed survival times.
2. The sequential methods considered are based on paired comparisons. If one of the patients in a pair drops out for any reason other than death from the disease studied, it will as a rule be useless to continue to keep the other one in the trial. This may cause a loss of efficiency in the sequential tests, which cannot occur with the χ^2 test.
3. Although the period required for the χ^2 test is, on average, longer than for the sequential tests, it is more constant. Variation in duration can only be caused by variation in intake. With the sequential tests, especially the open test, the variation in length of time required is much greater. Consequently, they may take longer than the χ^2 test.
4. Obviously organizing a trial using the χ^2 test, for which it is only necessary to determine the patient's condition a fixed time after starting the trial, is simpler than organizing a trial with a sequential sign test which requires that relevant changes in condition be registered immediately.

In this discussion we may further consider the average total number of patients which must be included in the trial before a decision can be reached. For the sequential tests this total is Tm (if m = required intake per year); for the χ^2 test, $(T - t_0)m$. If we calculate these numbers for the open sequential test and for the χ^2 test with $t_0/\bar{\mu} = 0.75$ and $t_0/\bar{\mu} = 1.0$, we always find that the values for the χ^2 test compared with the sequential test are lower where $t_0/\bar{\mu} = 0.75$ and very much lower where $t_0/\bar{\mu} = 1.0$. Admittedly these results are not entirely comparable, since the value for the open test is the average number required in the most unfavorable circumstances, but it does nevertheless appear that in this respect the χ^2 test is no less advantageous than the sequential test.

Our findings concerning the value of the χ^2 test for a 2×2 table, Wilcoxon's test and the sequential sign test for the analysis of clinical trials based on survival times may be summarized as follows.

1. The χ^2 test calls for the simplest organization of a trial and may be applied without specification of type of distribution of survival times. Further, this test is not unfavorable as regards duration of trials analysed. However, if one only wishes to minimalize the number of patients, irrespective of duration of trial, the χ^2 test is the least efficient method.
2. Wilcoxon's test for two samples is much more demanding as regards organization of the trial; for calculating the number of patients required the type of distribution of survival times must in principle be specified, although the number does not appear to depend greatly on this specification. In comparable cases, Wilcoxon's test requires considerably fewer patients than the χ^2 test. However, where duration is concerned,

Wilcoxon's test is by far the least efficient. In this respect preference may be given to variants of Wilcoxon's test, under which the trial may be discontinued after a fixed period T (see e.g. Efron, B. (1967)).

3. The sequential sign tests also require a more complicated organization of the trial than the χ^2 test. With these methods, not only the number of patients required but also the test criterion depends on the type of distribution of the survival times. For practical purposes, still more restricted schemes will have to be worked out. This might be worthwhile, since the sequential tests are particularly attractive if one wishes to restrict the trial as much as possible in regard to number of patients or duration, in case the methods of treatment compared should differ considerably from one another.

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ERRATA

On page VIII in Contents under Part VII '5. Duration of trial 194', read ... 201.

On page 23 in fourth par., second rule: 'On page 55', read: On page 56.
Ibidem in last rule of 6th par.: '(for a detailed calculation cf. Ch V § 2 p. 65)', read ... 67 .

On page 26 in second rule (above diagram): cf. Appendix table O4', read: ... table O8.

On page 32 beside the diagram: 'f Died of other cause than tumor', read: e Died etc.

On page 57 – In note instead of $\frac{100}{78.8}$ en $\frac{78.8}{100}$ read $\frac{100}{78.8}$ and $\frac{78.8}{100}$.

On page 76 first rule: In Ch. III § 3 p. 14', read: ... p. 15.

On page 139 in table f_c 43 in third item '<55 years' read: >55 years.

On page 173 in last column of table P instead of '0.67×10^3' read 6.7×10^3.

For statistical reason required number → S (χ^2 test for a 2 × 2 table, cf. table S1 Ch. 3 p. 17)

The number of therapies → t (t = 2 is used)

The percentage of incidence of the characteristic properties of patients which are considered of essential importance for the assessment of the therapies → $f_1\% \times f_2\% \times f_3\% \times f_0\% = F_n\%$ From this, the multiplicationfactor $\frac{100}{\%}$ can be calculated (cf. table $\frac{100}{\%}$ Appendix Part IV).

For the planning of the extent of the registration (cf. Ch. III § 6)

$$X_{c(linical)\ t(rial)} = S \times t$$

To determine the total number of patients suffering from the disease who must be available to make a particular trial possible (cf. Ch. III § 6)

$$X_{m(aterial)} = S \times t \times \frac{100}{F}$$

In case of a fixed number of available patients, to calculate the minimal percentage of incidence of characteristic elements in the material as a whole that is necessary to make the trial possible (cf. Ch. III § 6)

$$F_{min.} = \frac{100 \times t \times S}{X_m}$$

In order to determine the size of the entire female population necessary to make the trial possible (cf. Ch. III § 9)

$$X_{p(opulation)} = S \times t \times \frac{100}{F} \times \frac{(\frac{100}{P})}{q}$$

PART VII CONCISE REVIEW OF THE CALCULATION

STELLINGEN.

I.

Alvorens men overgaat tot de organisatie van een 'controlled clinical trial', dient men zich te bezinnen op de vraag of het aantal patiënten, dat in het betreffende rayon binnen een afzienbare termijn beschikbaar komt, voldoende zal zijn voor de uitvoering van de 'trial'.

II

Onderzoekingen betreffende de behandeling van patiënten met mammacarcinoom zullen betere resultaten geven, indien men betere methoden ontwikkelt om de uitbreiding van het ziekteproces exact te diagnostiseren.

III

Een goede samenwerking tussen statisticus en medicus onderling is van groot belang voor het kankeronderzoek.

IV

Op anatomische en physiologische gronden dient men, wanneer er een indicatie bestaat voor een lumbale sympathectomie wegens een éénzijdige arteriële doorbloedingsstoornis, deze ingreep dubbelzijdig te verrichten.

V

Arteriografisch röntgenonderzoek is slechts volledig, indien de serieopnamen in twee richtingen worden gemaakt. Slechts op deze wijze is het mogelijk de uitgebreidheid van subtotale afsluitingen van arteriën zuiver te beoordelen en eerst dan is een eventuele indicatie tot operatie exact te stellen.

VI

De éénzijdige everterende gastrointestinale anastomose is eenvoudig, veilig en doeltreffend.

Ravitch, M. M. et al.: Ann. Surg. 166:670, 1967.

VII

Bij anatomische repositie van een enkelfractuur, al dan niet met behulp van osteosynthese, wordt het resultaat niet beïnvloed door een tevoren bestaande luxatie van de talus.

VIII

Bij behandeling van fracturen van het os zygomaticum is repositie alleen meestal een onvoldoende therapie.
Aan de fixatie dient veel aandacht te worden besteed, waarbij de osteosynthese in de laterale orbitarand en de steuntampon in de sinus maxillaris in overweging moeten worden genomen.

IX

Ook bij afwezigheid van de karakteristieke cutane laesies moet een gedissemineerde lupus erythematodes als diagnose overwogen worden in gevallen, die gelijken op een rheumatische endocarditis en gepaard gaan met verschijnselen van een glomerulonephritis zonder hypertensie.

X

Longscanning draagt bij tot het vroeg stellen van de diagnose longembolie.
Bovendien wordt hierdoor later een objectieve beoordeling van de mate van herstel van de circulatie mogelijk.

Wagner, H. v.: Radiology Vol. 91 No. 6.

XI

Het verdient aanbeveling om instrumentarium dat met ethyleenoxyde is gesteriliseerd, geruime tijd aan de lucht bloot te stellen, teneinde het eventuele toxische ethyleenoxyde te verwijderen. Over de duur van dit proces en over de hoeveelheid ethyleenoxyde die achterblijft in verschillende soorten materiaal zijn geen exacte gegevens bekend.

The Medical Letter on Drugs and Therapeutics 1967, vol. 9 No. 7.

XII

De leiding in de medische technologie dient te worden toevertrouwd aan technische medici en niet aan medische technici.

XIII

Voor de verdere uitgroei en ontwikkeling van het ziekenhuiswezen in ons land is regionaal overleg en regionale samenwerking noodzakelijk.

XIV

De verwerking van kwik in tandheelkundig amalgaam kan mede milieuverontreinigend werken.

XV

Het in te stellen 'landelijk meetnet' voor het opsporen van luchtverontreiniging ('Trouw', 23 oktober 1971), is een zinloze perfektie, die slechts zal leren wat men al enige tijd weet: dat onze lucht verontreinigd is.

XVI

Wenn man nicht weiss, wie, was, warum,
dann gibt man immer valium.

Stellingen behorende bij het proefschrift 'Controlled Clinical Trials' door H. P. J. M. Beerepoot.
Nijmegen, 17 december 1971.